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VOL 142 NO. 12 DECEMBER 1988

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Monthly Circulation >44 500
Also published in French

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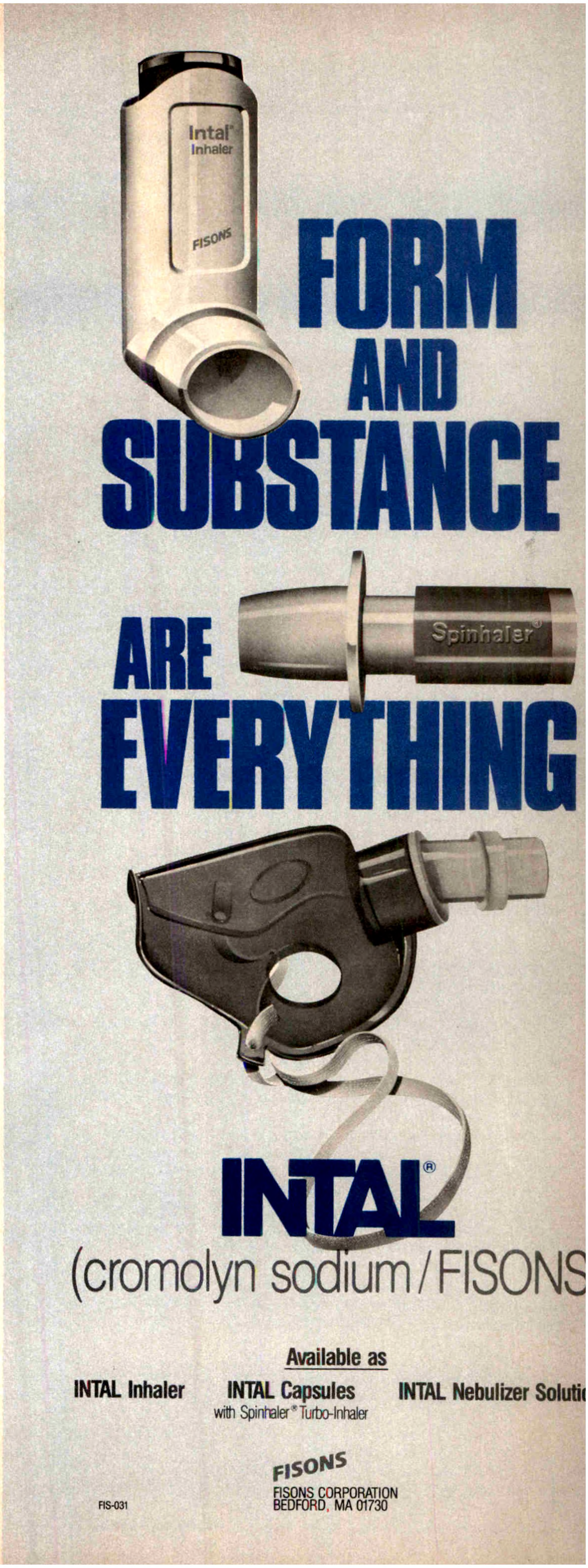

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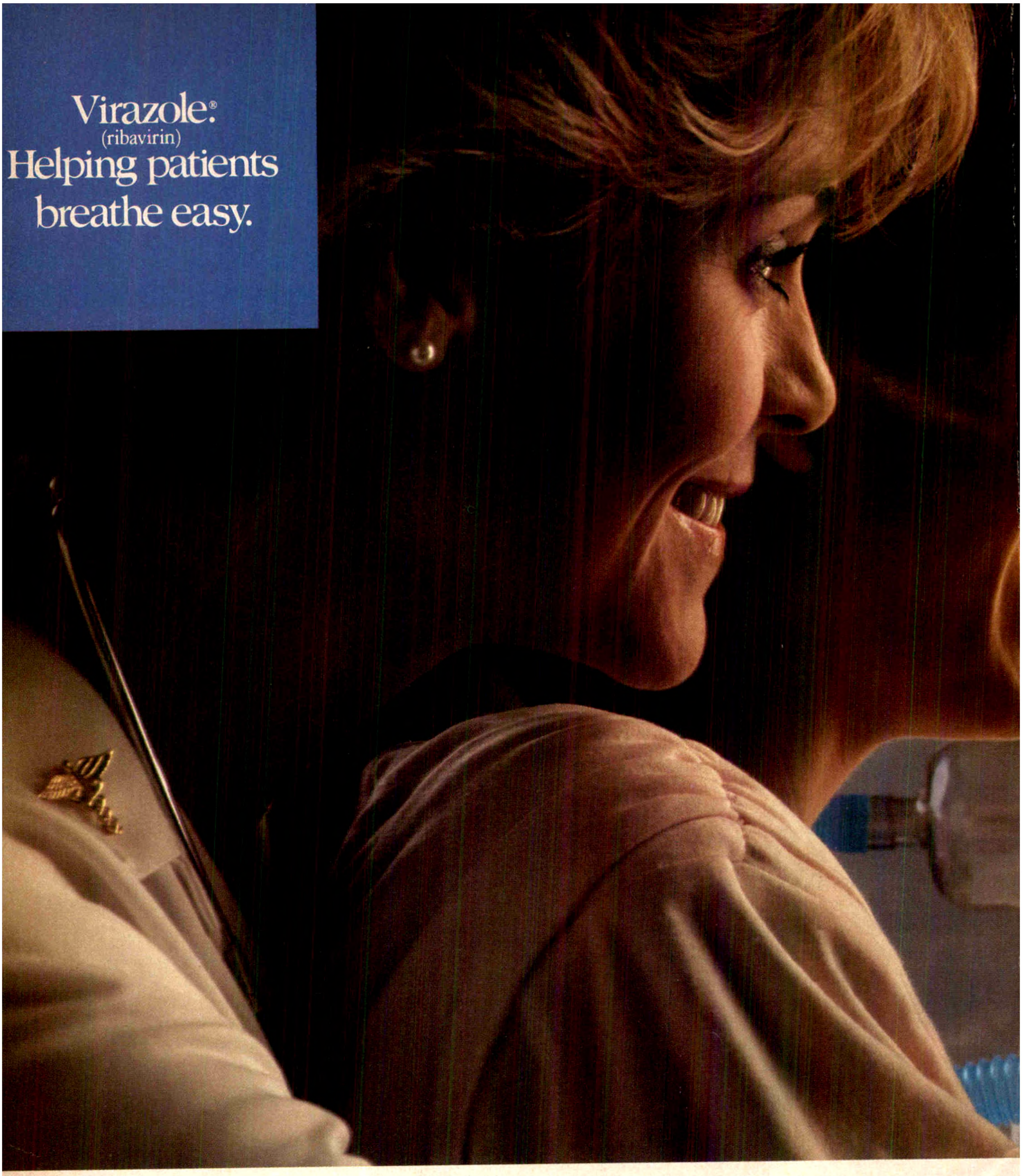

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Use of clinical parameters. *Pediatrics* 1988;81:22-26.

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VIRAZOLE® (ribavirin) aerosol is indicated for treatment of severe lower respiratory tract infections due to RSV in carefully selected, hospitalized infants and young children.

Breathe Easy

Virazole®
(ribavirin)

lyophilized for aerosol administration

PRESCRIBING
INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

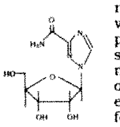
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole®(ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8μM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole®(ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

REFERENCES:

1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus *in vitro*. *Antimicrob Agents Chemother* 17:770-775, 1 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
3. Taber LH, Knight V, Gilbert BE, McClung HW et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory tract infection in infants. *Pediatrics* 72:613-618, 1983.
4. Hall CB, McBride JT, Walsh EE, Bell DM et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 308:1443-7, 1983.
5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.

January 1986
R-1-88

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The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

Oropharyngeal Examination for Suspected Epiglottitis

Sir.—I expect (and hope) that the report by Mauro et al[1] will not change the traditional approach of avoiding the *office* oropharyngeal examination of the child with suspected epiglottitis. Anecdotal or not, many pediatricians have seen (or know someone who has seen) a child with epiglottitis who had laryngospasm as a result of a tongue blade examination. I might risk venturing into waters where a shark lurks were I provided with a shark cage and an expert with a speargun; similarly, I might attempt an emergency department examination for suspected epiglottitis with an experienced intubator present. It does not seem that Mauro et al are suggesting we do otherwise.

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1. Mauro RD, Poole SR, Lockhart CH: Differentiation of epiglottitis from laryngotracheitis in the child with stridor. *AJDC* 1988;142:679-682.

Sir.—Since I have been present at the death or near death of several patients with epiglottitis, I feel constrained to respond to your request[1] and to the article by Mauro et al. I also wish to call attention to previous discussions of this subject.[2,3]

In none of the six patients with epiglottitis described by Mauro and colleagues was the epiglottis visualized by "light alone, simply asking the child to open his mouth." This is consistent with my own study[4] in which the epiglottis was visualized in none of three patients. That study was extended for several years and in no instance was the epiglottis visualized in a patient with epiglottitis when he or she was examined sitting up, with voluntary opening of the mouth, without a tongue blade. This procedure is nearly risk-free; none of my patients had acute dypsnea as a result of it.

In my view, however, the second step suggested by Mauro et al, ie, using the tongue depressor, carries substantial risk. Most children with epiglottitis will not cooperate when a tongue blade is used, and will give up their tripod position to push the blade away. They will then fall backward and may incur obstruction. Even if supported by an assist, this attempt at visualization will almost certainly increase anxiety and may lead to sudden obstruction. Cardiac arrest may occur and it may be difficult, if not impossible, to intubate and resuscitate the child in the emergency department.

Mauro et al also suggest that if the epiglottis is not visualized with the tongue depressor, laryngoscopy should be performed. Unless this is done by a person with extraordinary skill, the risks of acute obstruction are too great. Intubation of a child who has acute epiglottitis is very difficult and requires extraordinary control (usually provided in an operating room or, rarely, in a pediatric intensive care unit, where these skills have been demonstrated previously).

As I and others have noted, the risks of attempting to visualize the epiglottis may exceed the benefits. The diagnosis is usually easily made clinically by the experienced physician *without* direct examination. If an emergency department has physicians who are sufficiently knowledgeable and skilled to intubate emergently a patient with epiglottitis, these individuals will be able to suspect the presence of the disease and diagnose its probability. They then can proceed to the vital second step, the provision of an artificial airway, without delay. In a controlled situation (preferably in the operating room under the direction of an experienced endoscopist and anesthesiologist), the diagnosis can be confirmed and the patient's airway can be secured simultaneously.

I fear that the article by Mauro and colleagues will literally encourage inexperienced physicians to attempt to diagnose epiglottitis by inspection, thereby risking the patient's life. Lateral neck roentgenograms are accurate and reliable, but also delay placement of the airway. We have found them to be superfluous in patients suspected of having epiglottitis.

Twenty years ago, Baxter[5] showed in his own series of more than 100 patients with epiglottitis that provision of an airway on diagnosis was the key to reduction of mortality. It has been repeatedly demonstrated that any delay increases the chances of spontaneous or precipitated acute respiratory obstruction and cardiac arrest. Occasionally taking a patient to the operating room for airway placement and finding no epiglottitis is a small price to pay for the expeditious care of patients with epiglottitis. Aggressively examining the pharynx of a child in whom epiglottitis is a serious consideration is, in my view, similar to walking across the road with your eyes closed. You probably will get away with it, but it is very risky.

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1. Fulginiti VA: Acute supraglottitis (epiglottitis): To look or not? *AJDC* 1988;142:597.
2. Rapkin RH: Acute epiglottitis: Pitfalls in diagnosis and management. *Clin Pediatr* 1971;10:312.
3. Rapkin RH: Epiglottitis and the severe croup, in Smith CA, Dickerman JD, Lucey JF (eds): *The Critically Ill Child*. Philadelphia, WB Saunders Co, 1985, chap 1.
4. Rapkin RH: The diagnosis of epiglottitis: Simplicity and reliability of radiographs of the neck in the differential diagnosis of the croup syndrome. *J Pediatr* 1972;80:96-98.
5. Baxter JD: Acute epiglottitis in children. *Laryngoscope* 1967;77:1358-1367.

Sir.—We are concerned about both the safety and utility of direct inspection of the epiglottis in patients with suspected laryngotracheobronchitis, as reported by Mauro and colleagues.

They report no complications on direct inspection of the epiglottis in six children with acute epiglottitis. The exact upper 95% confidence limit for this proportion (0/6) is 35%.[1] This means that the study results are compatible with a complication rate as high as 35% for direct inspection of the epiglottis in patients with acute epiglottitis. Safety of the procedure certainly remains in doubt.

There is a rapid method to calculate the approximate upper 95% confidence limit when the number of occurrences in a study is 0.[2,3] If N is the number of study subjects, $3/N$ approximates the upper 95% confidence limit. When N is greater than 30, this approximation is accurate to one decimal place. For Mauro and colleagues' study, the approximate upper 95% confidence limit is 3/6, or 50%.

The initial clinical impression was laryngotracheobronchitis in 149 children, of whom two were found to have acute epiglottitis. The clinical history of these two patients should be presented in detail to help identify the factors that led to their initial misdiagnosis. Since these two patients had stridor and were without cough, and at least one of them was agitated, maybe it will be decided on careful review that their clinical presentation was more compatible with acute epiglottitis than laryngotracheobronchitis and that an anesthesiologist should have been present before the epiglottis was viewed. When acute epiglottitis is suspected, an anesthesiologist should be called. That protocol is followed by us, and the results of the study by Mauro et al do not support a change in that practice.

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1. Armitage P: *Statistical Methods in Medical Research.* Boston, Blackwell Scientific Publications Inc, 1981, p 114.
2. Hanley JA, Lippman-Hand A: If nothing goes wrong, is everything all right? *JAMA* 1983;249:1743-1745.
3. Rumke CL: Implications of the statement: No side effects were observed. *N Engl J Med* 1975;292:372-373.

Sir.—In their attempt to distinguish epiglottitis from laryngotracheitis, Mauro et al assessed 19 clinical findings, but they did not record the spontaneous position adopted by their patients. In our series of 30 children with epiglottitis, 14 (46%) adopted a characteristic sitting-up position and one (3%) adopted an all-fours position.[1] These peculiar positions, not described in viral croup and bacterial laryngotracheitis, and a temperature higher than 38.5°C, were the main signs of epiglottitis in our series (Table).

We agree with Mauro et al that the definitive diagnosis of acute epiglottitis requires direct inspection of the epiglottis. Of our 30 patients, 17 were transferred before intubation; inspection of the epiglottis was performed on restrained children in the sitting position, after ventilation with a mask and bag; we were able to view the epiglottis adequately, and no complications occurred. On the other hand, examination in the supine position seems very hazardous: before their admission, two of our 30 patients (6.5%) manifested apnea just after they were put into the supine position, and one of them died. We do not perform lateral neck roentgenograms because sending a child with epiglottitis to the radiology department increases the potential for sudden airway obstruction, and because the interpretation is equivocal if the roentgenograms are obtained at the bedside.

In a child who prefers to sit up, if supraglottitis is suspected because of a temperature greater than 38.5°C, absence of cough, and the presence of drooling, we have the following recommendations: (1) avoid inspection of the epiglottis at home; (2) transfer the child to an emergency department or an intensive care unit while in a sitting position, keeping in mind that children with epiglottitis can be given ventilatory assistance by mask and bag in case of marked respiratory distress[2]; and perform a direct examination of the epiglottitis in the presence of an experienced pediatric intubationist. The more cyanotic the child, the more dangerous is inspection of the epiglottis, and it must be performed after mask and bag oxygenation.

Clinical Findings in 30 Children With Epiglottitis[1]

Clinical Findings	No. (%) of Patients
Inspiratory dyspnea	30 (100)
Temperature >38.5°C	19 (63)
Sitting position	14 (46)
Four-stips position	1 (3)
Cervical lymphadenopathy	13 (43)
Dysphagia	7 (23)
Muffled voice	6 (20)
Hoarse voice	6 (20)
Drooling	6 (20)

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1. Leclerc F, Diependaele JF, Lemaire D, et al: Epilottites infectieuses de l'enfant. *Rean Soins Intens Med Urg* 1985;1:179-183.
2. Szold PD, Glicklich M: Children with epiglottitis can be bagged. *Clin Pediatr* 1976;15:792-793.

Sir.—The management of acute epiglottitis is rendered uncertain by the common use of the term *total* [or *complete*] *obstruction* in describing the pathogenesis of its disastrous consequence. Mauro et al recommend cautious direct examination to diagnose acute epiglottitis and minimize the danger of total airway obstruction. Were total obstruction a substantial risk, cautious direct examination might be appropriate, as it is following total obstruction due to the aspiration of a foreign body. In such circumstances time is available, labored respirations continue, circulation persists, and death is not abrupt.

There is no evidence, however, that total obstruction occurs in acute epiglottitis. Even those reports that call the feared deterioration total (or complete) obstruction uniformly describe the cessation of respiration and the frequently associated asystole.[1,2] The airway is still patent. Bag ventilation through an external mask is still effective[3,4] and is probably the optimal emergency procedure.[5,6] The problem is respiratory and cardiac arrest, not obstruction[7]: respiration and circulation have ceased, resuscitation must be immediate, and resuscitation may not be successful.

In any prolonged state of carbon dioxide retention and hypoxia, manipulation of the upper airway may result in a vagus-mediated apnea and bradycardia or cardiac arrest. When carbon dioxide retention and hypoxia result from acute epiglottitis, that likelihood seems dramatically increased (vagal sensitivity may be dramatically enhanced). If total obstruction (the epiglottis falling backward into the glottis) were the danger, direct examination by a pediatric house officer in an emergency department might be acceptable management. Inasmuch as it is not obstruction but reflex respiratory and cardiac arrest that is the danger, any manipulation before the induction of reflex-dampening, protective general anesthesia (associated with bag-and-mask ventilation) in an operating room is unjustified.[7-9] That the vast majority of children with acute epiglottitis recover regardless of management does not justify risking the lives of the few who are in danger.

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1. Bass JW, Fajardo JE, Brien JH, et al: Sudden death due to acute epiglottitis. *Pediatr Infect Dis* 1985;4:447-449.
2. Vernon DD, Ashok PS: Acute epiglottitis in children: A conservative approach to diagnosis and management. *Crit Care Med* 1986;14:23-25.
3. Kimmons HC, Peterson BM: Management of acute epiglottitis in pediatric patients. *Crit Care Med* 1986;14:278-280.
4. Blanc VF: Acute epiglottitis in children with special emphasis on anesthetic considerations. *Can Anaesth Soc J* 1977;24:1-7.
5. Glicklich M, Cohen RD, Zona JZ: Steroids and bag and mask ventilation in the treatment of acute epiglottitis. *J Pediatr Surg* 1979;14:247-251.
6. Szold PD, Glicklich M: Children with epiglottitis can be bagged. *Clin Pediatr* 1976;15:792-794.
7. Schloss MD, Gold JA, Rosales JK, et al: Acute epiglottitis: Current management. *Laryngoscope* 1983;93:489-493.
8. OH TH, Motoyama EK: Comparison of nasotracheal intubation and tracheostomy in management of acute epiglottitis. *Anesthesiology* 1977;46:214-216.
9. Outwater KM: Diagnosis and management of acute epiglottitis in children. *Crit Care Med* 1986;14:955-956.

Sir.—While I appreciate the trepidation some physicians might feel, the evaluation and recommendations by Mauro et al regarding the diagnosis of acute epiglottitis really ought not to be controversial. How many children have been unnecessarily subjected to, or have almost undergone, intubation for an incorrect diagnosis of acute epiglottitis? The first tenet of physical examination is inspection, not inference. I was taught the need for and safety in direct inspection of the epiglottis, using a good flashlight and sometimes a tongue depressor, by a wise and experienced senior attending pediatrician over 20 years ago.

As a purely personal preference in patient management, I would suggest the following compromise between the "do-lookers" and the "don't-lookers" when epiglottitis is suspected.

1. Mauro and colleagues' steps ([1] look with flashlight, with no instrument; and [2] look carefully, using a tongue depressor) should be sufficient. Use the tongue depressor, if needed, to depress the tongue firmly without placing the depressor all the way back so as not to touch the epiglottis. The wood is flexible, the familiar stick is not usually frightening to a child (unlike the strange, shiny, cold, hard laryngoscope), and the stick is less likely to traumatize the teeth or lips.
2. After a physician has seen and diagnosed acute epiglottitis, other persons should *not* look again. The next step for that frightened, air-hungry child is intubation.
3. If an initial, friendly, or gently coercive effort to visualize the epiglottis is *not* successful, do *not* attempt it with a frightened, struggling child in your office.
4. If the child is cyanotic, and a Heimlich or other maneuvers for inhaled food are not indicated, obtain the consultation of an anesthesiologist immediately, at an emergency department or a hospital intensive care unit. Humidified oxygen should be administered while waiting.
5. If the child is not cyanotic, ask that an anesthesiologist be made available, and proceed immediately to a roentgenogram (of the soft tissues of the neck as well as the chest) at the hospital for confirmation of a swollen epiglottis vs subglottic or tracheal edema, unsuspected foreign body, hemangioma, or even a retropharyngeal pouch or abscess. The patient, without waiting, should return directly to the emergency department or be admitted to an intensive care unit.
6. Since a negative radiologic examination does not rule out a nonopaque foreign body, the condition of an *afebrile* child might suggest the need for direct laryngoscopy or bronchoscopy.

May I leave the authors and your readers with a question? What sort of reasonably conservative consensus management is recommended for *early* epiglottitis, when the physician sees redness with only 2 to 3 mm of swelling/edema on looking in the throat of a child with fever, sore throat, and perhaps slight hoarseness?

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Sir.—I recently had the privilege of being requested to critique the article by Mauro and colleagues. Following are some of my thoughts.

This is an excellent article that really tries to shine light where we need it most.

The greatest limitation of this study is that it covers only six cases of acute epiglottitis. Therefore, no conclusion can be drawn regarding the safety and advisability of direct visualization of the epiglottis in these patients.

The authors should be encouraged strongly to continue their study until they have accumulated a meaningful number of acute epiglottitis cases so as to make conclusions regarding criteria for as well as the safety of the actual visualization.

Other means of visualization, such as the flexible nasopharyngoscope, should be included in that study.

Correlations of 19 criteria were examined and their predictive values for epiglottitis and laryngotracheitis were studied. Unfortunately, only three of the 19 criteria are specified.

Until the results of a continued study are known, the long-standing policy of performing visualizations only in surroundings that allow for an immediate and possibly difficult intubation is to remain the rule.

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Sir.—With regard to the article by Mauro et al on visualization in possible acute epiglottitis, I have the following comments.

First, a key point is that four of six cases of epiglottitis were correctly identified clinically, but two cases, presumably milder or of shorter duration, were incorrectly clinically classified.

My own preference in the first four cases would be to perform an examination in the operating room, but I see no inherent reason why a good examination could not be done in the emergency department with an anesthesiologist present. The major fault I find is with fools who waste valuable time on lateral neck films (the radiology department, as we all know, is absolutely the worst place in which a respiratory emergency could occur).

As for the two clinically misclassified cases, I have always made it a point to try to visualize the epiglottis in children with laryngotracheobronchitis and a low suspicion of epiglottitis, and certainly do so in all cases requiring racemic epinephrine and admission for observation. I can clearly remember one early case of epiglottitis diagnosed this way. Since these children are usually younger (Did the 12.9-year-old really have laryngotracheobronchitis?), I have no problem visualizing the epiglottis using a tongue blade with the patient either sitting or supine (Is there any reason to avoid supine examination with a tongue blade before proceeding to laryngoscopy?). In these cases, which again I presume are early, I doubt that major danger would accompany visualization.

Therefore, if there is a very high clinical index of suspicion of epiglottitis, examine only in a controlled environment, preferably an operating room, with an anesthesiologist and ear, nose, and throat specialist present. If probable croup with some suspicious signs is encountered, examine the patient before hospital admission for croup, with anesthesia available, as in Mauro and colleagues' design.

More extensive data would help, and I believe that this is an excellent subject for a multicenter cooperative study among major children's hospital emergency departments.

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Sir.—The article by Mauro and colleagues confirms an opinion I have held for 33 years of private pediatric practice. It has been my policy to examine the epiglottis visually in cases of croup to rule out epiglottitis, despite articles advising the substitution of a lateral neck roentgenogram for direct visualization. It is reassuring to find vindication in print.

My justification involves the following arguments:

1. The incidence of epiglottitis in my practice has not been the 4% reported by Mauro et al, but less than 0.1%. I have treated two cases in 33 years, compared with over 100 cases of croup annually. The hospital emergency department must receive the worst cases.
2. With the infant reclining and the neck extended, using a tongue depressor (I use narrow "Popsicle" sticks that are thicker and bend less easily than adult tongue depressors), a quick look elicits either a view of the epiglottis or the posterior pharynx. Since in acute epiglottitis swelling is always present, if the epiglottis is absent in a good view of the pharynx then epiglottitis is not present.
3. I receive instantaneous reassurance that an emergency is not at hand. Epiglottitis, on the other hand, is such an emergency that delays in visiting the radiology department are potentially hazardous. Moreover, my experience agrees with the literature that roentgenography is far from 100% accurate.
4. I have a feeling that, like other coughs, calls for treatment of croup are more common at night when the radiology department is short-staffed and there is no radiologist to read the film. Taking roentgenograms, then, requires 90 minutes of my time, compared with an office visit of 15 minutes, for I must accompany the patient to the emergency department and read the roentgenogram myself.
5. For these reasons I approve of the teaching that physical examination, and not a lateral neck roentgenogram, should be the examination of choice in croup and epiglottitis.

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Sir.—In 32 years of pediatric experience I have routinely examined the epiglottis in all children with laryngeal symptoms. The epiglottis can almost always be seen with the patient in the sitting position, with or without the use of a tongue depressor. I have detected four or five cases of epiglottitis without immediate respiratory compromise and, to my knowledge, I have not overlooked any.

I have never been associated even peripherally with a case of diagnosed bacterial tracheitis.

Robert Clark III, MD
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Sir.—I agree with the findings of Mauro and associates. For the past 26 years I have used similar criteria and protocols for assessing the supraglottis. I have not observed any incidence of vasovagal responses nor have I observed trauma to the mouth, as described by Mauro et al. This may be because of my long-term relationship with my patients and their parents and several substantial differences in technique.

The parent and the child are asked to sit on my treatment room table. The child sits up on his parent's lap and is asked to "pant like a puppy" and keep his chin down (neck flexed). If this cannot be accomplished an adult restrains the child by pressing the child's arms onto the sides of his head as he lays on the table with his head flexed on a cushion. I have found that an indirect laryngoscopy is much less traumatic and much quicker than application of force against a resistant tongue. I use a wide-angle laryngeal mirror heated with an alcohol lamp to prevent fogging. The child is intrigued by the flame and then shown that the mirror, though warm, is not hot. Yes, most children do understand. The mirror is carefully inserted *paramedially*, usually without benefit of a tongue blade or tongue pressure, while the child sometimes attempts to pant. A directed gag reflex, *carefully avoiding the midline*, is frequently necessary. The mirror is easily angulated so that the entire epiglottis can be visualized. This contrasts to the sometimes-limited view obtained by simply using the tongue blade and light.

The savings to the child in time, radiology costs, trauma, and other expenses are obvious. I do not perform this procedure in the office or at the hospital until personnel and equipment are set up in preparation for an emergency procedure.

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Sir.—I graduated from medical school in December 1943. After internship, the Army, and residency, I began full-time solo pediatric practice and have been in it ever since.

In my early days I never heard of *not* examining a child for epiglottitis if it was suspected, so I did it then and I have done it ever since. Of course, I write because I have never had one bit of trouble. I do not know how many patients with this condition I have seen in my 44 years in practice, but I am sure I have seen my share. Never has one patient given me any more trouble than does a patient undergoing a routine throat examination.

Recently, a patient of mine was admitted through the emergency department late at night. Because of "croupiness," a soft-tissue roentgenogram of the neck was obtained. The report was "some narrowing consistent with epiglottitis." All hospital resident staff members were afraid to look into the throat, so the patient was admitted to the intensive care unit with full epiglottitis precautions.

I saw the patient the next day, looked into the throat, found no epiglottitis, and wrote the discharge.

We have now become so paranoid about not looking into the throat, even for simple croup, that we have probably gone too far. Of course I feel it is relatively safe to do so, and I am sure I will continue to attempt to visualize the epiglottis in all cases of croup with or without the classic signs of epiglottitis.

I agree with Mauro and colleagues and I applaud you for bringing up a discussion on such an important subject.

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Sir.—I concur with Mauro and colleagues' evaluation of patients with acute supraglottitis. I have evaluated all patients whom I have suspected of having this problem by visual inspection as benignly as possible using a tongue blade. I have not incurred any substantial sequelae by doing this and in the process I have diagnosed approximately seven to ten cases of epiglottitis over the past 17 years.

Obviously, one cannot predict whether problems will occur during future observations by this method. However, I wanted to add my opinion and experience to this issue.

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Sir.—On the issue of acute supraglottitis, I vote with Mauro et al. As a physician-educator, I have maintained appointments in family medicine and emergency medicine during the past ten years. The avoidance of traumatic or forceful manipulation is a fact of life. Lateral soft-tissue roentgenograms of the neck have been overrated, even though every lecturer shows one slide of a grossly deformed epiglottis. By the time I see these children, in literally every case the tongue has been depressed (ie, step 2 of Mauro and colleagues' protocol). Anecdotally, there have been no known complications during the past ten years.

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Sir.—I have always believed that one of the worst suggestions ever given to the private practitioner was that of diagnosing epiglottitis by a lateral neck film. Probably the worst place to take a patient with epiglottitis would be down a long hall to the radiology department, with all the associated trauma, fear, and suspense.

For 25 years I have looked, in the office, for epiglottitis, usually just with a tongue depressor and penlight and occasionally with a laryngoscope. The epiglottis is usually easily visible and the diagnosis is rapidly made or ruled out, at no expense and with no emotional trauma. Carefully done, there is little gagging and no more distress than the patient has already experienced.

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Sir.—First, I must comment on a nonmedical point. The word *epiglottitis* is in common parlance; why therefore indulge in the dubious sport of newspeak in writing about something called *supraglottitis*? This does not serve the purpose of clarity of communication.

Mauro and colleagues have clearly defined some of the issues. The largest issue of all is that the vast majority of acutely stridulous children do not present themselves to emergency departments but rather to the offices of their physicians. Half of these physicians, I would anticipate, are not pediatricians. What are the realistic alternatives? The currently taught dictum of not looking and certainly not touching (no tongue blade) leads to both underdiagnosis and oversuspicion. One result is the risk of epiglottitis progressing to a critical and life-threatening state before being recognized; the other result (and just as serious an issue although not so immediate) is the vast overuse of emergency departments and the enormous overexposure of young children to irradiation of the neck.

If only the lateral neck roentgenogram were the panacea that some assert it to be! Clearly the decision on epiglottitis vs laryngotracheitis can most often be resolved on clinical grounds, relying on historical data, clinical examination, the presence of and quality of cough, and the quality of voice changes, among other signs. Even so, it is wonderfully reassuring to have the additional support of direct visualization of the epiglottis. The main reason to look and to examine carefully but completely is to exclude a diagnosis of acute epiglottitis. Failure to differentiate leaves one with the untenable assumption that every child with acute stridor has acute epiglottitis until proven otherwise and the consequence of that position is gross overmanagement. The object is obviously to reduce to the barest few the number of cases presenting a dilemma, without any loss of sensitivity.

I have been looking at epiglottises for 30 years and I must agree in principle with Mauro and colleagues on the need for direct visual inspection. I have collected no data but I am sure that my experience with acutely stridulous children during those years far exceeds the 155 cases reported by Mauro and colleagues and cannot be dismissed as merely annecdotal. Mauro et al did their work in a hospital emergency department, which afforded them certain obvious safety nets. I doubt that anyone would advise laryngoscopic examination in any position in the private office as a diagnostic procedure (nor are they suggesting as much).

We ask the child to sit up and lean forward with the chin forward and the neck extended. With nothing more than that and a wide-open mouth most epiglottises may be seen. The tongue blade, if used carefully to sweep the tongue downward and forward while looking from above, will greatly increase the percentage of successful examinations. This position is similar to the laryngoscopy posture and it is probable that we accomplish almost the same visualization by this means as did Mauro et al, short of the ultimate supine laryngoscopic examination. If suspicion of epiglottitis still exists, it is time for a change in venue and use of all customary measures.

One has only to witness the usual management of acute epiglottitis in emergency rooms—the avoidance of adequate clinical examination, the overuse and often erroneous overinterpretation of lateral neck roentgenograms—to realize the necessity of resolving this diagnosis. Good history and good physical examination, the cornerstones of all medical diagnosis, apply here as well as to all other areas of clinical medicine. Other means are merely accessory. It is unfortunate that the lessons that we teach to inexperienced trainees and that are designed as rules and protocols to protect the patient clearly substitute for the judgment to which some are born and which develops in most others with time.

Mauro and colleagues' data suggest that the absence of spontaneous cough is the most reliable historical factor for differentiating acute epiglottitis from laryngotracheitis. The use of this criterion overestimated the incidence of acute epiglottitis by 22 cases in a pool of 155. The examination without supine laryngoscopy resolved the diagnosis to virtually the same degree. What would be the diagnostic accuracy of examination without supine laryngoscopy if the patient population were reduced to those not presenting without spontaneous cough? Could all or most of the children without spontaneous cough be differentiated into component groups by physical examination, thereby obviating the need for roentgenograms in most cases?

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We are not using "newspeak" in designating supraglottitis *as the correct term for infection of the supraglottic structures.* Epiglottitis *has been in use because of the mistaken notion that only the epiglottis is involved in this infection; that is not the case. The aryepiglottic area and other supraglottic structures may be involved, without involvement or with minimal involvement of the epiglottis, but with the same effect, ie, obstruction of the upper airway. Thus, we prefer the more correct term* supraglottitis *to remind us of the possibility of the breadth of possible involvement.*

Dr Mauro has responded to previous letters covering the additional points that you raised in your letter. I agree that he did not advise that we examine such children in any position in the office as a diagnostic procedure. However, the fact that we have seen children arrive at our institution near death or already dead as a result of examination of the throat by uninformed or inexperienced attendants in another emergency department argues for us to present both sides of the coin.—Ed.

In Reply.—We thank the many *AJDC* readers who responded to our recent article and to Dr Fulginiti's editorial. Of the 15 correspondents, ten wrote to agree with our approach and four to disagree, and one commentator took an intermediate position. We have certainly achieved our goal of stirring debate regarding a widely proclaimed but poorly substantiated tenet of medical dogma.

Of the four dissenting correspondents, none challenged the efficacy of our approach. All wrote to say that six cases of epiglottitis were not sufficient to demonstrate our approach's safety, a point with which we agree, and that we made explicitly in our report. On the other hand, as we also noted in our report, the medical literature contains abundant opinion but hardly any objective data to suggest that our approach is dangerous. Of course, we *believe* that our approach is safe and reasonable, but we were not interested in arguing our beliefs in a scientific forum. To expand on Dr Fischer's metaphor: when you have swum for years in waters that are alleged to be infested with sharks, and you have never even seen a shark, much less been bothered by one, you begin to suspect that the danger has been overstated.

Until more data are available, it will be each practitioner's responsibility to assess the likely risks and benefits of our approach. We do regret having terminated our study before larger numbers of children with epiglottitis were included. We will now endeavor to continue the direct-inspection aspect of our study.

It seems from their letters that the dissenters to our strategy have overlooked two critical elements. First, we inspect the epiglottis in the absence of an anesthesiologist only when the examining pediatrician thinks that croup is the likely diagnosis. Second, it is utterly meaningless to speak of the risk of "looking" without also considering the risk of not looking. In our scheme, the risk, however real or of whatever magnitude, of looking without an airway specialist present exists only for the child with clinically unapparent epiglottitis. If one chooses not to inspect that child's epiglottis, what will one do? The patient will either be sent home or will be admitted to the hospital with the diagnosis of croup. Either event is the disaster that our method seeks to avoid.

Is it preferable to take all children with equivocal presentations to the operating room for inspection? We think such an approach is impractical, as stridor is a common symptom. Indeed, in 1972 Dr Rapkin also thought it impractical. In considering ". . . those patients who are unlikely to have epiglottitis, but in whom it should be ruled out . . .",[1] he noted: "In our hospital and in most community hospitals [airway specialists] are not so readily available. The pediatrician is often alone in the evaluation of the patient with croup syndrome."[1] Dr Rapkin's answer to the dilemma then was to recommend a lateral neck roentgenogram, which, in 1988, he finds "superfluous." Our answer is to inspect carefully the epiglottis.

Dr Havens wonders whether other physicians would have mistaken epiglottitis for croup, as we did in two patients before inspection of the epiglottis. His point is well taken if he is questioning whether such an error in clinical judgment would be made in one third of cases (two of six, in our study). That number is poorly estimated; such an event is likely to occur less frequently in a large series. But his call for more detailed information regarding these two patients is not helpful, unless he is prepared to present a scheme that will permit identification of children with epiglottitis in 100% of cases, without recourse to direct inspection. Whether or not a given physician would have been misled by these two patients, surely there will be others whose clinical presentation will be ambiguous.

Drs Leclerc and Martinot suggest providing supplemental oxygen before inspection of the epiglottis. We agree; since completing our study, we have changed our protocol to include two minutes of mask oxygenation preceding inspection. We are very interested in Leclerc and Martinot's report of two patients in whom apnea developed immediately after they were placed in a supine position. If prospective, Leclerc and Martinot's would be the first such study that we have encountered that documents a serious complication temporally related to an attempt to inspect the epiglottis.

Dr Walker, in a puzzling letter, asserts that the risk of pharyngeal manipulation is not total airway obstruction, but rather is respiratory and cardiac arrest, presumably of metabolic origin or mediated through the vagus nerve. In support of this view, he cites nine articles, six of which explicitly mention total airway obstruction as the complication to be feared. Two give no mention at all of the likely mechanism, and one mentions both theories as possible. All nine references present opinion, with no data cited that are germane to the question.

Dr Rosefsky asks for a conservative approach to the treatment of a child with very early epiglottitis. If convinced that the child has epiglottitis, even very early, we still recommend standard care, including provision of a secure airway via nasotracheal intubation. An expectant approach (watchful waiting) is too risky. If the appearance of the epiglottis is equivocal, we might observe the child for an hour or two in a pediatric intensive care unit and inspect the epiglottis again.

In response to Dr Bellens' inquiry, the 16 items from the history and physical examination that were not associated with the final diagnosis are listed in the text of our report (page 680). Dr Lathrop offers his personal experience that epiglottitis has been absent whenever the epiglottis cannot be seen with a wooden tongue depressor alone. We are reluctant to accept this criterion as reassuring, since we could not view the epiglottis with a tongue blade alone in four of our six patients with epiglottitis. Dr Fischer is correct that we have no prospective data regarding inspection of the epiglottis in the office, and we are not advocating it. Two of us (R.D.M. and S.R.P.), however, did use this approach while in office practice for a combined total of ten years, with two cases of epiglottitis detected and no adverse consequences. In addition, eight of the ten supportive letters to the editor were written by office-based practitioners with more than 197 years of combined experience, without mishap.

We close with an anecdote of our own. Recently, one of us (R.D.M.) encountered an infant in our emergency department who had acute stridor. After two or three minutes of observation, it appeared that the child probably had epiglottitis. The infant was left sitting with his mother, and his pharynx was not examined. An anesthesiologist was called and arrived within five minutes, just as the child suffered an abrupt, obstructive, respiratory arrest. The anesthesiologist examined the epiglottis, found it to be inflamed, and intubated the infant without complication.

Had we examined that child's epiglottis before calling the anesthesiologist, the *assumption* would have been that pharyngeal manipulation had caused the respiratory arrest. We speculate that many (but probably not all) other extant anecdotes also represent the rapid natural progression of epiglottitis, and not diagnostic misadventures.

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1. Rapkin RH: Radiographic examination in epiglottitis. *J Pediatr* 1972;81:1036-1037.

Successful Urokinase Therapy for Superior Vena Cava Syndrome in a Premature Infant

Sir.—Thrombosis and infection are serious complications of central venous catheterization.[1] Treatment with thrombolytic agents and antibiotics given through the central catheter has yielded variable results.[1-3] We treated an infant of very low birth weight who developed thrombosis, infection, and superior vena cava (SVC) syndrome as complications of the insertion of a central venous catheter. The infant was successfully treated with a continuous peripheral intravenous infusion of urokinase.

Patient Report.—A 760-g male infant was delivered by cesarean section at 26 weeks' gestation; he had Apgar scores of 2 at 1 minute and 7 at 5 minutes. The immediate neonatal course was complicated by hyaline membrane disease that required endotracheal intubation and assisted ventilation.

At 6 days of age a Broviac catheter (Davol/Bard, Cranston, RI) was inserted via the facial vein into the right internal jugular vein to facilitate venous access and to provide parenteral nutrition. The infant received 15% to 20% dextrose, 2.5 g/kg/d of protein, and 2.5 g/kg/d of soybean oil emulsion through the central line. In addition, the infusate contained 0.5 U/mL of heparin sodium.

At 19 days of age the infant developed an elevated white blood cell count and an increase in the number of band cells. A blood culture was obtained and was positive for methicillin-resistant *Staphylococcus aureus*. The infant was given vancomycin hydrochloride through the central line. However, a subsequent blood culture was again positive for methicillin-resistant *S aureus* and the central line was removed.

Two days after removal of the catheter, the infant developed SVC syndrome manifested by marked edema of the head and neck. A two-dimensional echocardiogram was obtained and it disclosed a large clot in the SVC. Since the central line was no longer in place, peripheral intravenous infusion of urokinase was begun. Initially, the infant was given 6000 U/kg of urokinase as a bolus and then a continuous infusion of 6000 U/kg/h was begun. Also, fresh-frozen plasma (10 mL/kg) was given every 12 hours. Coagulation studies performed before urokinase administration was begun disclosed a prothrombin time of 11.7 s (control, 10.8 s), a partial thromboplastin time (PTT) of 69 s (control, 30 s), and a fibrinogen level of 3.5 g/L. After urokinase therapy was begun, the prothrombin time and PTT were essentially unchanged, but the fibrinogen level fell to 1.1 g/L and the level of fibrin degradation products rose to greater than 40 mg/L. The fibrinogen level remained low and levels of fibrin degradation products remained elevated throughout the course of urokinase therapy.

An echocardiogram obtained one day after initiation of urokinase therapy showed extension of the clot into the right atrium (Fig 1). The dosage of urokinase was then increased to 8000 U/kg/h and serial echocardiograms were obtained. Clinical improvement was noted, with complete resolution of the SVC syndrome three days after the institution of urokinase therapy. Therapy with this fibrinolytic agent was continued for a total of ten days, at which time the echocardiogram showed the thrombus to be much smaller, with central cavitation (Fig 2). After the urokinase therapy was ended, a continuous infusion of heparin was begun to maintain the PTT at 1.5 times the normal value for the next 11 days, at which time the clot had completely resolved. A follow-up echocardiogram ten days after heparin therapy was discontinued showed no thrombus in the SVC or right atrium.

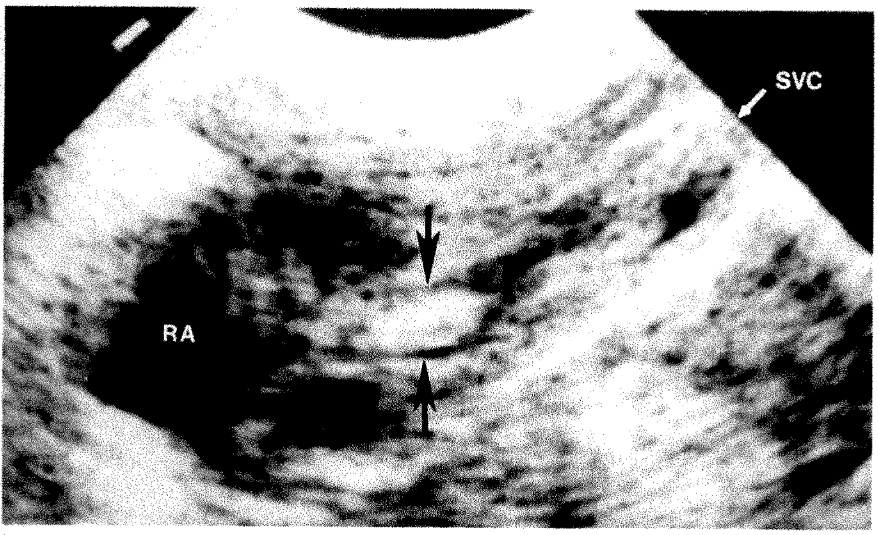

Fig 1.—Two-dimensional echocardiographic frame taken along right, high, parasternal long axis demonstrates clot (arrows) within superior vena cava (SVC). Clot extends into right atrium (RA) and up SVC.

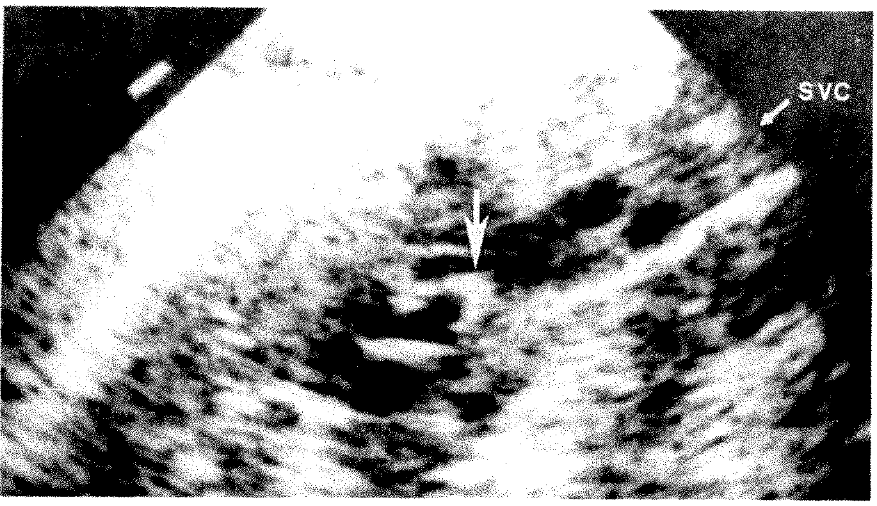

Fig 2.—Two-dimensional echocardiographic frame taken along right, high, parasternal long axis shows that clot (arrow) within superior vena cava (SVC) has decreased in size and central cavitation in clot has developed.

Comment.—Urokinase is a thrombolytic agent that converts plasminogen to plasmin.[4] Plasmin then digests fibrin, causing a reduction in plasma concentrations of fibrinogen and an increase in fibrin degradation products.[4] This therapeutic action of dissolving fibrin is not limited to the unwanted thrombus, and hemorrhage may thus occur as a complication,[4] although it did not occur in our patient. We used levels of fibrinogen and fibrin degradation products throughout the duration of urokinase therapy as indicators that a lytic state had indeed been induced and found persistently decreased levels of fibrinogen and increased levels of fibrin degradation products. A previous study has indicated that there is a decreased amount of plasminogen present in neonates, thus reducing the effectiveness of fibrinolytic therapy.[4] While urokinase was being administered we also gave fresh-frozen plasma every 12 hours to provide plasminogen so that optimal lysis of the thrombus with our fibrinolytic therapy would occur.

Streptokinase is another thrombolytic agent that has been used in neonates.[2] We chose to use urokinase because it is nonantigenic, has fewer side effects, and has a more predictable dose-response relationship.[4] Our patient had no appreciable side effects from therapy.

Although the experience with both drugs is limited, urokinase and streptokinase have been used for thrombolysis in infants in varying dosages and with variable results.[1-5] Recently, Sadiq et al[1] reported successful thrombolysis in eight of nine thrombotic episodes when urokinase was administered through a central venous catheter. Also, Olsen et al,[2] using streptokinase, were able to dissolve a right atrial thrombus by applying the thrombolytic agent directly in the clot. In contrast, however, Corrigan et al[5] noted no effect from urokinase infusions on aortic thrombi. While most experience has been with local administration of a fibrinolytic agent into the thrombus, the peripheral intravenous route has been used.[4]

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1. Sadiq HF, Devaskar S, Keenan WJ, et al: Broviac catheterization in low birth weight infants: Incidence and treatment of associated complications. *Crit Care Med* 1987;15:47-50.
2. Olsen MM, Blumer JL, Gauderer WL, et al: Streptokinase dissolution of a right atrial thrombus. *J Pediatr Surg* 1985;20:19-21.
3. Haffer AAM, Rench MA, Ferry GD, et al: Failure of urokinase to resolve Broviac catheter-related bacteremia in children. *J Pediatr* 1984; 104:256-258.
4. Corrigan JJ Jr: Neonatal thrombosis and the thrombolytic system: Pathophysiology and therapy. *Am J Pediatr Hematol Oncol* 1988;10: 83-91.
5. Corrigan JJ Jr, Jeter M, Allen HD, et al: Aortic thrombosis in a neonate: Failure of urokinase thrombolytic therapy. *Am J Pediatr Hematol Oncol* 1982;4:243-247.

Age-Independent Anthropometric Criteria in the Assessment of PEM

Sir.—Protein-energy malnutrition (PEM) in preschool children is a major public health problem in developing countries. The severe forms of PEM are clinically discernible, but the mild and moderate forms require anthropometry for their detection. Several anthropometric criteria have been used for the grading of nutritional status of the community, but there is controversy as to their effectiveness. Few studies have compared the effectiveness of these methods.[1-3] In the present study, we compare the various anthropometric methods for their ef-

Table 1.—Different Anthropometric Criteria Used in Assessing PEM*

Criteria†	Source, y	Degree Normal	Mild		Moderate	Severe
Weight-for-height, %	Shakir,[5] 1972	>90	80-90		70-80	<70
Height-for-age, %	McLaren,[10] 1982	>95	90-95		85-89	<85
Midarm circumference, cm	Shakir,[5] 1972	13.5		12.5-13.5		<12.5
Kanawati and McLaren index (midarm and head circumferences), cm	Kanawati and McLaren,[6] 1970	0.31	0.28-0.31		0.25-0.28	<0.25
Body mass index, Rao's index (weight/height)^2 (100)						
Criterion 1	Rao and Singh,[7] 1970	1.5	1.35-1.49		(Mild to moderate)	<1.35
Criterion 2	Rao and Singh,[7] 1970	1.6	1.35-1.50		(Mild to moderate)	<1.35
Dugdale's index (weight/height)(1.6)(100)	Dugdale,[8] 1971	0.88-0.97	0.83-0.88		0.79-0.83	<0.79
Indian Academy of Pediatrics Degree	Indian Academy of Pediatrics,[9] 1974	Normal	1st	2nd	3rd	4th
%		>80	71-80	61-70	51-60	<50

*PEM indicates protein-energy malnutrition.
†Criterion 1 considers 0.15 as a normal value and values of 0.14 or less as indicative of PEM; criterion 2 considers 0.16 as the normal value.

Table 2.—Percentage of Distribution of Malnourished Children as Determined by Various Criteria

Criteria*		No. (%) of Malnourished Children Normal	Mild	Moderate	Severe	Total Malnourished, %
Weight-for-height		216 (42.9)	176 (34.9)	65 (12.9)	47 (9.3)	57.1
Height-for-age		104 (20.6)	128 (25.4)	104 (20.6)	168 (33.4)	79.4
Midarm circumference		232 (46.0)	. . . . . .	112 (22.2)	160 (31.8)	54.0
Kanawati and McLaren index (midarm and head circumference)		64 (12.7)	177 (35.1)	231 (45.9)	32 (6.3)	87.3
Rao's index (criterion 1) (body mass index: [weight/height]^2[100])		288 (57.1)	. . . . . .	112 (22.2)	104 (20.6)	42.9
body mass index (criterion 2)		160 (31.1)	. . . . . .	240 (47.7)	104 (20.6)	68.3
Dugdale's index		192 (38.1)	96 (19.0)	104 (20.6)	112 (22.2)	61.9
Indian Academy of Pediatrics Grade	**Normal**	**I**	**II**	**III**	**IV**	
	136 (26.9)	99 (19.7)	163 (32.3)	51 (10.2)	55 (10.9)	73.1

*Criterion 1 considers 0.15 as a normal value and values of 0.14 or less as indicative of protein-energy malnutrition; criterion 2 considers 0.16 as the normal value.

ficiency in determining PEM by assessing their sensitivity and specificity indexes as well as their predictive values, taking weight-for-height as the reference method.[1]

Subjects and Methods.—Five hundred four preschool children residing in three slums of Davangere, India, were studied. Their ages were determined by use of a pretested "local calendar."[4] Their height, weight, midarm circumference, and head circumference were recorded by standard methods.[4] Table 1 shows the different anthropometric criteria used in the present study.[5-9]

Body mass index (Rao's index) was divided into two criteria. The first criterion considered a value of 0.15 as normal and 0.14 or less as evidence of PEM.[7] The

Table 3.—Percentage of Malnourished Children as Determined by Use of Different Criteria of Assessment, in Decreasing Order of Percentage Detection

Criteria Used*	No. (%) of Children Normal	Malnourished
Kanawati and McLaren (midarm and head circumference)	64 (12.7)	440 (87.3)
Height-for-age	104 (20.6)	400 (79.4)
Indian Academy of Pediatrics	136 (26.9)	368 (73.1)
Body mass index: criterion 2	160 (31.7)	344 (68.3)
Dugdale's index	192 (38.1)	312 (61.9)
Weight for height	216 (42.9)	288 (57.1)
Midarm circumference	232 (46.0)	272 (54.0)
Body mass index: criterion 1	288 (57.1)	216 (42.9)

*Criterion 1 considers 0.15 as a normal value and values of 0.14 or less as indicative of protein-energy malnutrition; criterion 2 considers 0.16 as the normal value.

Table 4.—Sensitivity, Specificity, and Predictive Values of Various Methods to Detect PEM*

Criteria†	Sensitivity, %	Specificity, %	Predictive Values, %	
			Positive	Negative
Kanawati and McLaren (midarm and head circumferences)	97.7	25.9	63.6	87.5
Height-for-age	88.9	33.3	64.0	69.2
Indian Academy of Pediatrics	88.5	47.7	69.3	75.7
Body mass index: criterion 2	85.8	55.1	71.8	74.4
Dugdale's index	80.6	77.8	82.9	75.9
Midarm circumference	78.1	74.5	80.3	71.9
Body mass index: criterion 1	58.3	77.8	77.8	58.3

*PEM indicates protein-energy malnutrition.

†Criterion 1 considers 0.15 as a normal value and values of 0.14 or less as indicative of PEM; criterion 2 considers 0.16 as the normal value.

second criterion considered a value of 0.16 as normal and 0.15 or less as evidence of PEM.[7]

Tables 2 and 3 show the distribution of children according to their nutritional status, as determined by the use of various criteria.

Since weight-for-height indicates the current nutritional status of the child,[1] this measurement was taken as an indicator of true malnutrition in the community, and the sensitivity and specificity indexes and the positive and negative predictive values of various other criteria were calculated taking weight-for-height as a reference.[1] The results are shown in Table 4.

Comment.—We concluded that midarm circumference [Shakir] and Dugdale's index were useful anthropometric criteria in the evaluation of PEM of preschool children in the community. Their sensitivity, specificity, and positive and negative predictive values were of a high order (78.1%, 74.5%, 80.3%, 71.9%, 80.6%, 77.8%, 82.9%, and 75.9%, respectively). Both methods are effective and age independent, and they do not need the use of costly equipment and standard growth charts. Moreover, both methods can easily be taught to health care workers in rural areas, urban slums, or remote tribal settlements.

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1. Sood AK, Kapil U: Anthropometry in detection of protein-energy malnutrition. *Indian Pediatr* 1984;21:635-639.
2. Malik A, Malhotra A, Ahmad SH: Age-independent criteria for detection of protein-energy malnutrition. *Indian Pediatr* 1984;21:213-216.
3. Sen V, Purohit BK, Jain TP: Weight/height^2 ratio in assessment of protein-caloric malnutrition. *Indian Pediatr* 1980;17:135-138.
4. Jelliffe DB: *The Assessment of the Nutritional Status of the Community,* World Health Organization, Monograph Series No. 53, Geneva, World Health Organization, 1966, pp 59-78.
5. Shakir A: Pattern of protein-energy malnutrition in young children attending an outpatient clinic in Baghdad. *Lancet* 1972;2:143-146.
6. Kanawati AA, McLaren DS: Assessment of marginal malnutrition. *Nature* 1970;228:573-575.
7. Rao V, Singh K: An evaluation of the relationship between nutritional status and anthropometric measurements. *Am J Clin Nutr* 1970;23:83-93.
8. Dugdale AE: Age-independent anthropometric index of nutritional status. *Am J Clin Nutr* 1971;24:174-176.
9. Report of Nutrition subcomittee of the Indian Academy of Pediatrics. *Indian Pediatr* 1974;9:360-366.
10. McLaren DS: Protein-energy malnutrition (PEM), in McLaren DS, Burman D (eds): *Textbook of Paediatric Nutrition,* ed 2. New York, Churchill Livingstone Inc, 1982, p 107.

Maternal Floor Infarction: An Unusual Cause of Intrauterine Growth Retardation

Sir.—Maternal floor infarction (MFI) is an uncommon placental lesion associated with stillbirth and intrauterine growth retardation, with an apparent high rate of recurrence in subsequent pregnancies.[1-3] The condition has been infrequently discussed in the obstetric or pathology literature, and essentially no information is available in pediatric or genetic journals.

Patient Report.—A 690-g male infant was born after a 36-week gestation. His birth length was 31.0 cm, and his head circumference was 26.0 cm. He had first-degree hypospadias, bilateral cryptorchidism, inguinal hernias, and bilateral bridged palmar creases. No other minor or major anomalies and no specific malformation syndrome were identified. Blood IgM levels, cytomegalovirus, herpes virus, and toxoplasmosis titers, and chromosomal analysis results were normal. The placenta weighed 155 g and showed extensive fibrosis on the maternal surface. Microscopic sections of the placenta confirmed the diagnosis of MFI.

The patient's parents are nonconsanguineous and in good health. The mother's blood pressure remained normal throughout the pregnancy. She has had three previous gestations: the first was terminated by therapeutic abortion; the second resulted in death of twins at the 22nd gestational week with uterine size estimated to be 14 weeks, and the third gestation resulted in fetal death at seven weeks.

Comment.—The term *maternal floor infarction* was first applied to this particular syndrome by Bernirscke and Driscoll[1] in 1967. It is not a completely satisfactory term because it does not represent a true infarction.[3] Maternal floor infarction is characterized by diffuse and marked thickening of the basal plate or maternal floor of the placenta. The maternal surface appears white to pale gray and is unusually smooth. The thickening results from deposits of considerable amounts of fibrin within and adjacent to the decidua basalis. No evidence of chronic inflammation or hemolytic disease is seen.[1,3] The pathogenesis of this disorder is obscure. It is unrelated to maternal toxemia and does not appear to have an inflammatory or infectious cause.[1,2]

Maternal floor infarction is an important cause of recurrent late fetal loss.[1-3] Floor infarcts were diagnosed in 4.8 of 1000 placentas in the Collaborative Perinatal Study.[3] Fifty percent of the gravida mothers with floor infarctions compared with 27% of the controls had prior abortion or stillbirth. Maternal floor infarction has been reported in association with nine reproductive failures in one woman[1] and five consecutive instances of fetal death in late pregnancy in another woman (K. Bernirscke, MD, written communication, May 1980). The mother's reproductive history is not typical in that MFI is usually associated with third-trimester fetal loss.[1-2]

An accurate diagnosis of the cause of recurrent late pregnancy fetal loss and/or intrauterine growth retardation is extremely important. A circulating anticoagulant, with or without active systemic lupus erythematosus, has been shown to be a treatable cause of recurrent second- and third-trimester fetal loss.[4] Ten of the ten women described by Lubbe et al,[4] had a positive antinuclear antibody test result, an elevated activated partial thromboplastin time, and an elevated Kaolin clotting time. The major placental finding reported for this disorder was multiple scattered infarcts in various stages of evolution, with some placentas also showing intervillous thrombosis and fibrin deposition.[4] The placenta in our case report showed MFI and no recent infarction. In addition, the mother had a negative blood antinuclear antibody test result and a normal activated partial thromboplastin time. Recognition of MFI will enable appropriate genetic counseling of the parents, ensure careful monitoring of subsequent pregnancies, and provide further information regarding the cause and potential treatment of this disorder.

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1. Bernirscke K, Driscoll SG: Maternal floor infarction, in Bernirscke K, Driscoll SG (eds): *Pathology of the Human Placenta.* New York, Springer-Verlag NY Inc, 1967, pp 328-330.
2. Clewell WH, Manchester DK: Recurrent maternal floor infarction: A preventable cause of fetal death. *Am J Obstet Gynecol* 1975;121:346-347.
3. Naeye RL: Maternal floor infarction. *Hum Pathol* 1985;16:823-828.
4. Lubbe WF, Butler WS, Palmer PJ, et al: Lupus anticoagulant in pregnancy. *Br J Obstet Gynecol* 1984;91:357-363.

Measles in Hospitalized African Children With Human Immunodeficiency Virus

Sir.—Due to the increasing number of children infected with the human immunodeficiency virus (HIV), there has been concern regarding the interaction of HIV and endemic childhood diseases.[1,2] Measles is a major cause of childhood morbidity and mortality in Africa. Attack rates reach 100% in unvaccinated children, and estimates of fatality rates range from 2% to 34%. Although measles vaccine is recommended by the World Health Organization for all children at 9 months of age in developing countries, questions have been raised about the use of this live viral vaccine in HIV-infected children. The decision to use the vaccine depends on its safety and efficacy as well as on the risk and severity of measles disease in these children. Since measles can be severe in immunocompromised children, concomitant HIV and measles infection may be associated with increased morbidity and mortality. To investigate the severity of measles in HIV-infected children, we studied hospitalized patients with measles in Kinshasa, Zaire.

Table 1.—Characteristics of Hospitalized Measles Patients

Characteristic	Human Immunodeficiency Virus Status: Seropositive	Human Immunodeficiency Virus Status: Seronegative	Total
No. (%) of patients	16 (5.1)	298 (94.9)	**314**
Age, mo			
Median	11	12	12
Range	4-23	4-60	4-60
Males, No. (%)	10 (62.5)	159 (53.4)	**169** (53.8)
Vaccinated, No. (%)	3 (18.8)	70 (23.5)	**73** (23.2)
Adenopathy, No. (%)	6 (37.5)	84 (28.2)	**90** (28.7)
Muscle wasting, No. (%)*	10 (62.5)	72 (24.2)	**82** (26.1)
Diarrhea, No. (%)	8 (50.0)	149 (50.0)	**157** (50.0)
Pneumonia, No. (%)	11 (68.8)	166 (55.7)	**177** (56.4)
Altered mental status, No. (%)	2 (12.5)	57 (19.1)	**59** (18.8)
Corneal lesions, No. (%)	0	24 (8.1)	**24** (7.6)
Subcutaneous emphysema, No. (%)	0	12 (4.0)	**12** (3.8)
Stomatitis, No. (%)	1 (6.3)	17 (5.7)	**18** (5.7)
Otitis media, No. (%)	4 (25.0)	52 (17.5)	**56** (17.8)
White blood cell count, × 10^9/L			
Median	8.5	10.8	10.8
Range	3.3-39.1	2.5-45.9	2.5-45.9
Hematocrit			
Median	0.282	0.281	0.281
Range	0.219-0.394	0.127-0.446	0.127-0.446
Lymphocyte count, × 10^9/L			
Median	4.2	3.4	3.4
Range	0.3-13.0	0.4-19.8	0.3-19.8

*Relative risk = 2.4; 95% confidence interval, 1.1-fold to 3.8-fold increased risk.

Table 2.—Measles Case Fatality Rate

	Human Immunodeficiency Virus Status					
	Seropositive			Seronegative*		
Age, mo	**No. of Deaths**	**No. of Patients**	**Case Fatality Rate**	**No. of Deaths**	**No. of Patients**	**Case Fatality Rate**
0-4	1	3	33.3	1	1	100.0
5-8	0	5	0	21	83	25.3
9-14	0	1	0	30	94	31.9
15-19	2	5	40.0	13	38	34.2
20-24	2	2	100.0	9	21	42.9
25-60	...	0	...	9	55	14.5
0-8	1	8	12.5	22	84	26.2
≥9	4	8	50.0	60	208	28.8†
Total	5	16	31.3	82	292	28.1

*Six patients with an unknown outcome are excluded.
†Relative risk = 1.7; 95% confidence interval, 0.5-fold to 3.0-fold increased risk of death.

Patient Reports.—Three hundred fourteen children 5 years of age or younger admitted to the measles ward at Mama Yemo Hospital and Kalembe Lembe Hospital between January and March 1987 were enrolled. Blood was obtained from all patients on admission for total white blood cell counts and differentials and hematocrit and serologic testing. Sera were tested for HIV antibody by enzyme-linked immunosorbent assay (Wellcozyme, Burroughs Wellcome, Beckenham, England) and Western blot analysis (DuPont Inc, Wilmington, Del). A random sample of 120 specimens was tested for measles IgM antibody by enzyme-linked immunosorbent assay (MA Bioproducts, Walkersville, Md).

On admission, interviews were conducted with the parent or guardian using a standardized form to obtain information regarding the child's medical history, including vaccination status, and the course of the present measles illness. Physical examinations were performed on admission and every four days during hospitalization. Characteristics evaluated included the following: adenopathy, muscle wasting, diarrhea, laryngitis, subcutaneous emphysema, otitis media, stomatitis, pneumonia, altered mental status, and corneal lesions.

The median age of enrolled children was 12 months (Table 1). The median time between the onset of measles and admission was four days (range, one to 24 days). Ninety-one percent of patients tested had measles IgM antibody. Children were hospitalized for a median of four days (range, one to 39 days).

Sixteen children (5.1%) were HIV seropositive (Table 1). Age, sex, and vaccination status did not differ between HIV-seropositive and -seronegative children. Clinical characteristics and laboratory findings on admission were similar, except for muscle wasting, which was significantly more frequent in HIV-seropositive children.

Eighty-seven deaths occurred among the 308 patients with a known outcome (case fatality rate, 28.2%) (Table 2). Eighty-eight percent of deaths, including all those in HIV-seropositive children, were attributed to pneumonia, and 12% to diarrhea. There was no overall difference in case fatality rates between HIV-seropositive (31.3%) and -seronegative (28.1%) children. Among children 9 months of age or older, the case fatality rate in HIV-seropositive children was higher than in HIV-seronegative children (four [50.0%] of eight vs 60 [28.8%] of 208); however, this difference was not statistically significant. Unvaccinated seropositive children 9 months of age or older had a 2.5-fold increased risk (95% confidence interval, 0.9-fold to 3.2-fold increased risk) of dying compared with unvaccinated HIV-seronegative children (four [80.0%] of five vs 45 [32.1%] of 140). Among HIV-seropositive children in this age group, there was a trend toward lower mortality in vaccinated compared with unvaccinated children (0 [0%] of three vs four [80.0%] of five).

None of the admission clinical characteristics, including muscle wasting, was associated with fatal outcome. Lymphopenia (an absolute lymphocyte count $<2 \times 10^9$/L) was associated with an increased risk of dying in the hospital for both HIV-seropositive (relative risk = 6.7; 95% confidence interval, 0.9-fold to 172-fold increased risk) and -seronegative (relative risk = 1.8, 95% confidence interval, 1.1-fold to 2.6-fold increased risk) children, but this was significant only in the latter group.

Comment.—In this study the case fatality ratio in hospitalized patients with measles was high (28.2%), but it is similar to those reported in other hospital-based studies in Africa. No difference in the overall case fatality rate between HIV-seropositive and -seronegative children was observed. Since only severely ill patients with complications are admitted to the hospital in Kinshasa, hospitalized children with measles may be so severely ill that no difference in measles mortality could be detected between HIV-infected and -uninfected children. However, among children 9 months of age or older, a trend was found for a higher fatality rate in children with HIV infection. The lack of difference in younger children may have been due to the fact that some were not infected but had transplacentally acquired antibody. Although the numbers were small among HIV-seropositive and -seronegative children, lower case fatality rates were observed in vaccinated compared with unvaccinated children. This suggests that vaccination may reduce the measles case fatality rate, a finding reported in other studies.[3] However, this finding may have been confounded by better access to medical care or better prior health in the vaccinated group.

The observed difference in the case fatality rate between seropositive and seronegative children 9 months of age or older may be due to the progression of HIV infection causing more severe immunosuppression in older children. Although children who died were more likely to be lymphopenic, since measles infection itself can decrease lymphocyte counts and because lymphopenia was associated with an increased risk of fatal outcome for seronegative children in this study, the lymphopenia cannot be attributed totally to HIV infection.

Our study was limited by the small number of HIV-seropositive measles cases by the fact that it was a hospital-based study and because there was limited assessment of malnutrition, which has been associated with increased measles mortality. The inability to distinguish symptomatic from asymptomatic HIV infection also limited the interpretation of findings. Although children with clinical acquired immunodeficiency syndrome may be expected to have more severe measles, the severity of measles in children with asymptomatic HIV infection is not known.

While questions remain concerning the safety and efficacy of measles vaccine in HIV-infected children, some data indicate that measles vaccine is not associated with adverse reactions in these children.[4] This study suggests that measles is more severe in HIV-infected children and supports the World Health Organization's recommendation that since measles infection is almost universal among unvaccinated children in developing countries, these children should receive measles vaccine regardless of HIV status.[2,5]

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1. Rogers MF: AIDS in children: A review of the clinical, epidemiologic, and public health aspects. *Pediatr Infect Dis* 1985;4:230-236.

2. Von Reyn CF, Clements CH, Mann JM: Human immunodeficiency virus infection and routine childhood immunization. *Lancet* 1987;2:669-672.

3. Aaby P, Bukh J, Leerhoy J, et al: Vaccinated children get milder measles infection: A community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-863.

4. McLaughlin M, Thomas P, Onorato I, et al: Use of live viral vaccines in HIV infected children: A retrospective survey. *Pediatrics* 1988;82:229-233.

5. Expanded Programme on Immunization: Global advisory group: Immunization of children infected with HIV. *WHO Wk Epidemic Rec* 1987;62:5-9.

CP 24,239

High-Dose Intravenous Methylprednisolone for Childhood Idiopathic Thrombocytopenic Purpura

Sir.—I have read with interest Halperin and Doyle's article[1] and Corrigan's editorial[2] about bone marrow examination in idiopathic thrombocytopenic purpura (ITP). I would like to add a few points.

The authors do not mention that bone marrow examination also excludes megaloblastic anemia, which rarely presents with thrombocytopenia.

Corrigan[2] states that "there is no laboratory test that is diagnostic of ITP in children." I believe that antiplatelet antibody determination by the modified Handin and Stossel method[3] would serve this purpose. So far, antibodies have been determined in 177 acute cases (90 in the thrombocytopenic phase, 87 in remission, and 54 cases in both conditions) and in 55 chronic cases (35 in the thrombocytopenic period, 20 in remission, and eight cases in both conditions) of ITP. It was also studied in 126 controls (67 patients without hematologic disorders and 59 thrombocytopenic controls: 28 patients with leukemia, ten with aplastic anemia, ten with Fanconi's aplastic anemia, and 11 with sepsis and thrombocytopenia). Platelet antibodies were detected at presentation and in remission in all patients with ITP but in none of the controls. Antiplatelet antibody levels were higher statistically in the thrombocytopenic phase than in remission in both acute and chronic cases. In three chronic and one acute cases of ITP, the elevation of the antibody level during relapse was also demonstrated.

Age, Sex, and Improvement Time of Patients With Thrombocytopenia*

	High-Dose Intravenous Methylprednisolone	Oral Prednisone (2 mg/kg)	Untreated
No. of patients	16	16	17
Mean age, mo (range)	46 (3-156)	64.5 (19-132)	77.5 (19-156)
Male-female ratio	11:5	10:6	7:10
No. (%) of patients in whom platelet level $>150 \times 10^9/L$ at particular time during treatment			
Day 3	11 (68.7)	. . .	. . .
Week 1	13 (81.2)	3 (18.7)	2 (11.7)
Week 2	15 (93.7)	5 (31.2)	5 (29.4)
Week 4	16 (100)	7 (43.7)	12 (70.5)
Up to 4 mo	. . .	7 plus 2 with partial remission	14 plus 1 with partial remission

*Partial remission is defined as a platelet count greater than $100 \times 10^9/L$ but less than $150 \times 10^9/L$.

When the treatment of ITP (acute as well as chronic cases) is mandatory, I believe that high-dose intravenous (IV) methylprednisolone therapy is the best choice.[4,5] In a controlled study, I have found that the results of oral prednisone treatment (2 mg/kg) are not different from those in untreated patients. But with high-dose IV methylprednisolone therapy (30 mg/kg daily for three days, 20 mg/kg daily for four days, and subsequently 10, 5, 2, and 1 mg/kg daily for one week each; each dose administered for two to five minutes), the platelet count would be normal ($>150 \times 10^9/L$) on the third day of treatment in almost 69% of the patient group, while nearly 94% of the patient group would reach a normal level in two weeks (Table). High-dose IV methylprednisolone therapy has also been used successfully in the treatment of different hematologic disorders.[6-9]

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1. Halperin DS, Doyle JJ: Is bone marrow examination justified in idiopathic thrombocytopenic purpura? *AJDC* 1988;142:508-511.
2. Corrigan JJ Jr: Bone marrow examination and idiopathic thrombocytopenic purpura. *AJDC* 1988;142:487.
3. Özsoylu Ş, Allahverdi H, Lâleli Y, et al: Platelet survival in childhood idiopathic purpura in remission. *J Pediatr* 1976;89:388-390.
4. Özsoylu Ş: High-dose intravenous methylprednisolone for the treatment of childhood chronic idiopathic thrombocytopenic purpura. *Pediatr Rev Commun* 1987;2:29-40.
5. Özsoylu Ş, Irken G, Karabent A: High-dose intravenous methylprednisolone for acute childhood idiopathic thrombocytopenic purpura. *Eur J Haematol*, in press.
6. Özsoylu Ş: Bolus methylprednisolone for refractory Diamond-Blackfan syndrome. *Lancet* 1984;2:1033.
7. Özsoylu Ş, Coşkun T, Minassezzi S: High-dose intravenous glucocorticoid in the treatment of childhood-acquired aplastic anemia. *Scand J Haematol* 1984;33:309-316.
8. Özsoylu Ş, Ruacan S: High-dose intravenous corticosteroid treatment in childhood idiopathic myelofibrosis. *Acta Haematol* 1986;75:49-51.
9. Özsoylu Ş: High-dose intravenous methylprednisolone in treatment of recessive osteopetrosis. *Arch Dis Child* 1987;62:214-215.

In Reply.—Thrombocytopenia may, as suggested by Dr Özsoylu, accompany megaloblastic anemia; rarely, it can precede the onset of overt anemia. To our knowledge, however, thrombocytopenia does not precede those early and more specific blood smear changes such as granulocytic hypersegmentation or erythrocytic macro-ovalocytosis, which characterize megaloblastic anemia.[1] Likewise, the mean erythrocyte corpuscular volume is increased early in the course of megaloblastic anemia, as well as in various forms of marrow failure. Hence, our recommendation to include the peripheral blood smear examination and the mean corpuscular volume among those parameters on which the decision to perform a bone marrow aspiration in a suspected case of ITP is taken.

The usefulness of platelet serology in the diagnosis of ITP has recently been addressed in an editorial, the title of which leaves little doubt as to its conclusions: "Are Platelet-Antibody Tests Worthwhile?"[2] We agree with Dr Özsoylu that some tests detecting platelet-associated antibodies may be very sensitive. The problem has been, for over three decades, to find one equally specific. In this respect, Dr Özsoylu's data are not representative of the findings of many other workers in the field. For instance, von dem Borne et al,[3] who detected platelet antibodies in almost 100% of patients with ITP, also found such antibodies in 68.5% of 92 patients with thrombocytopenia associated with a variety of diseases (eg, malignant disorders, infections, toxemia of pregnancy, and alcoholism). As a result, platelet serology has a high negative predictive value (approximately 95%) but a rather low positive predictive value for ITP (approximately 50%). In other words, one can probably safely rule out ITP in a patient who has no detectable platelet antibodies, but diagnosing ITP on the basis of a positive serologic test would be as accurate as flipping a coin.

Finally, the treatment issue raised by Dr Özsoylu goes beyond the scope of our original article. Suffice it to say that the rapid increment in platelet counts observed with high-dose intravenous corticosteroids can also be achieved with oral prednisone at a dose of 4 mg/kg/d and that intravenous gamma globulin has a similar effect[4] with a much shorter duration of therapy (one to four days) and, more importantly, with fewer side effects.

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1. Lanzkowsky P: Clinical, pathogenetic, and diagnostic considerations of vitamin B_{12} deficiency and other congenital and acquired disorders, in Nathan DG, Oski FA (eds): *Hematology of Infancy and Childhood*, ed 3. Philadelphia, WB Saunders Co, 1987, pp 344-362.
2. Harrington WJ: Are platelet-antibody tests worthwhile? *N Engl J Med* 1987;316:211-212.
3. Von dem Borne AEGK, van der Lelie H, Vos JJE, et al: Antibodies against cryptantigens of platelets. *Curr Stud Hematol Blood Transf* 1986;52:33-46.
4. Blanchette VS: High-dose intravenous immunoglobulin therapy in childhood acute idiopathic thrombocytopenic purpura, in Waters AH, Webster HDB (eds): *Intravenous Immunoglobulins in Immunodeficiency Syndromes and Idiopathic Thrombocytopenic Purpura.* London, The Royal Society of Medicine, 1985, pp 71-82.

Minor Malformations: Significant or Insignificant

Sir.—Dr Hoyme[1] in his editorial published in the September issue of *AJDC* failed to recognize our[2] recent work regarding the value of minor malformations for predicting the presence of a major malformation. In our study, 4305 newborn infants were examined for the presence of minor anomalies and major malformations. There were 158 infants identified as having three or more minor anomalies, among whom 31 (19.6%) had a concomitant major malformation. Our observed predictive value of 19.6% differs substantially from the 90% reported by Marden et al[3] and cited by Hoyme. A similar predictive value of 26% was noted in a similar study by Mehes et al.[4] In reviewing these studies, the most likely cause for this difference is the use of a checklist of minor anomalies in our study. This checklist helped remind our examiners to look for the presence or absence of each specific minor feature in every one of our patients. Marden et al[3] did not have a standardized method for recording their observations. We believe that the presence of three or more minor anomalies is only 20% predictive for major malformations, yet some minor anomalies remain essential to the early recognition of several serious malformation syndromes. Based on our findings, parents of infants with three or more minor anomalies can be counseled on more optimistic terms and their physicians can be tempered by their clinical impression of the child before proceeding with extensive investigative studies for occult major malformations.

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1. Hoyme HE: Minor malformations: Significant or insignificant? *AJDC* 1987;141:947.
2. Leppig KA, Werler MM, Cann CI, et al: Predictive value of minor anomalies: *J Pediatr* 1987;110:539-547.
3. Marden PM, Smith DW, McDonald MJ: Congenital anomalies in the newborn infants, including minor variations. *J Pediatr* 1964;64:357-371.
4. Mehes K, Mestyan J, Knoch V, et al: Minor malformations in the neonate. *Helv Paediatr Acta* 1973;28:477.

Dr Hoyme did not respond.—Ed.

Perinatal Factors and Separation Time of the Umbilical Cord

Sir.—With regard to the statement by Novack et al[1] that they are unaware of any study in developed countries on the effects of perinatal factors on the time of umbilical cord separation, we wish to point out that we have already published such a study.[2]

Our study was carried out on a group of 911 infants born in the Netherlands. The perinatal factors we studied included the sex of the infant, its gestational age and birth weight, and the method of delivery, whether by cesarean section, vaginal delivery with the aid of forceps or ventouse, or unassisted vaginal delivery. We also studied the effects of the presence or absence of septicemia or other infections necessitating treatment with antibiotics and the presence or absence of jaundice in the newborn that required treatment with phototherapy. The effects of other various medical neonatal problems that necessitated admission to the Special Care Baby Unit (such as asphyxia of the newborn, hypoglycemia, and hypocalcemia) were studied together.

The method of cord care during the study was that which is commonly used in the Netherlands. A dry gauze dressing was applied around the umbilical stump and an umbilical binder was used. The infants were bathed daily beginning at 12 hours of age.

The time of cord separation in our group ranged from one to 29 days (mean, 7.4 days; SD, 3.3 days). This clearly differs from the times reported by Novack et al[1] but compares more closely with times of cord separation reported in other larger studies: Tötterman and Autio[3] reported a mean time of cord separation of 6.3 days in 600 Finnish neonates and Bhalla et al[4] found a mean time of cord separation of 5.8 days in 840 Indian infants.

Despite the earlier time of cord separation in our study, we also found a similar delay (2.1-day [SE, 0.33-day]) in cord separation in those infants born by cesarean section compared with those infants born vaginally. Delivery with the aid of forceps or ventouse did not substantially affect the time of cord separation. A relationship was also found between the gestational age of the infant and the time of cord separation: the shorter the gestational age the later the cord separated. The birth weight of the infant was also related to the time of cord separation: the lower the birth weight the later the cord separated. However, in our study it was not possible to separate completely the effect of birth weight from the effect of gestational age. The time of cord separation was also affected by the sex of the infant, with cord separation occurring earlier in female than in male infants. An interesting finding of our study was that cord separation was delayed when the infant suffered from septicemia or other infections that necessitated treatment with antibiotics. No relationship was found between the time of cord separation and the other factors studied, including jaundice treated with phototherapy in the newborn or other medical neonatal problems for which the infant was admitted to the Special Care Baby Unit.

From the results of our study[2] and that by Novack et al[1] it appears that some perinatal factors influence the time of separation of the umbilical cord and that this separation time is independent of the cord-care regimen being used.

The exact mechanism of separation of the umbilical cord is still not clear. The timing of this event is influenced by perinatal events as well as leukocyte function, and probably by many more as yet unknown factors.

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1. Novack AH, Mueller B, Ochs H: Umbilical cord separation in the normal newborn. *AJDC* 1988;142:220-223.
2. Oudesluys-Murphy AM, Eilers GAM, de Groot CJ: The time of separation of the umbilical cord. *Eur J Pediatr* 1987;146:387-389.
3. Tötterman LE, Autio S: Treatment of the umbilical cord of the newborn. *Acta Obstet Gynecol Scand* 1970;49:57-59.
4. Bhalla JN, Nafis N, Rohatgi P, et al: Some observations on separation of the umbilical stump in the newborn. *Indian J Paediatr* 1975;42:329-334.

In Reply.—We appreciate the letter from Drs Oudesluys-Murphy and de Groot calling our attention to their article. We regret not having had the opportunity to review their data, which corroborate many of the findings in our study, such as the association of cesarean section with delayed separation of the umbilical cord. They report a shorter duration between delivery and cord separation (which is consistent with other data) when no antibiotic or antiseptic procedure is instituted as part of the routine umbilical cord care of the newborn, an observation consistent with other reports, as noted in our original publication.

Their study included all infants admitted to the normal newborn and neonatal intensive care units, while our study specifically excluded infants admitted to the neonatal intensive care unit. Their finding of delayed separation with decreased birth weight and gestational age does not exclude the effects of antibiotics (those infants treated with antibiotics had a delay of 2.95 days) or method of delivery. These variables were not controlled when examining the effects of gestational age and birth weight on umbilical cord separation.

Thus, it would appear that migration of neutrophils, or phagocytic cells, into the umbilical stump is the major variable that accounts for the duration between birth and the cord separation. Perinatal events that inhibit infiltration of the cord (eg, systemic antibiotics or local "antiseptics"), abnormal function of phagocytic cells, delay in separation of the cord, and those events that enhance infiltration decrease the interval between birth and cord separation.

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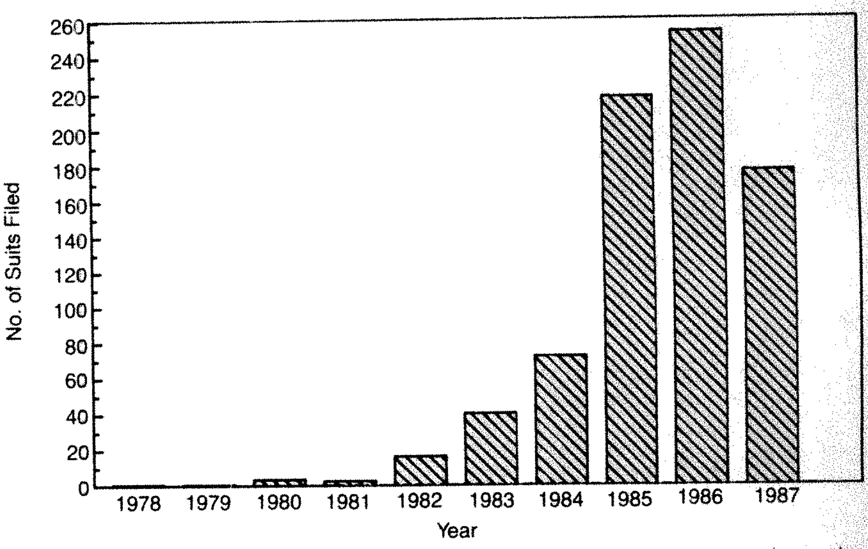
DTP Vaccine Litigation Update

Sir.—My 1986 article[1] summarized the experience of the three manufacturers of diphtheria and tetanus toxoids and pertussis (DTP) vaccine from 1978 through 1985. I recently obtained summary information from the manufacturers about their experiences in 1986 and 1987. The results are shown in the Table. The number of doses of DTP vaccine distributed in the United States stayed relatively constant during that time. The number of suits filed reached a peak in 1986, with 255 filed, and declined to 178 in 1987 (Figure). As in previous years, somewhat more than half of the suits specified an amount sought. In 1986, the specified amount sought totaled nearly $2.2 billion; this declined to $1.2 billion in 1987. The average amount sought de-

DTP* Vaccine Distribution and Suits Filed in the United States

Year	Doses Distributed, Millions	Suits Filed	Suits per Million Doses	Suits Specifying Amount	Amount Claimed, Millions of $	Amount Per Suit, Millions of $
1978	17.99	1	0.056	1	10	10.00
1979	18.41	1	0.054	0	...	...
1980	21.81	4	0.183	4	43	10.75
1981	18.82	3	0.159	2	25	12.50
1982	18.82	17	0.903	10	414	41.40
1983	18.79	41	2.182	27	655	24.26
1984	16.18	73	4.512	28	1303	46.54
1985	19.79	219	11.066	120	3162	26.35
1986	19.43	255	13.121	131	2193	16.74
1987	20.46	178	8.700	96	1276	13.29
Total	**190.50**	**792**	4.157	**419**	**9081**	21.67

*DTP indicates diphtheria and tetanus toxoids and pertussis.



Suits filed against manufacturers of diphtheria and tetanus toxoids and pertussis vaccine in United States from 1978 through 1987.

creased progressively from 1984 through 1987.

The cause for the decline in the number of suits filed in 1987 is not known with certainty; however, there is speculation that the reduction may be related to anticipation of implementation of the National Vaccine Injury Compensation Program, which took effect on Oct 1, 1988. Only time will tell whether this program will bring about a permanent reduction in the number of suits brought against the manufacturers.

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1. Hinman AR: DTP vaccine litigation. *AJDC* 1986;140:528-530.

Relation of Bone Mineralization Measures to Serum Biochemical Measures

Sir.—Harkavy[1] discussed the theoretical benefits of reporting bone mineral content (BMC) measurements (mg/cm) in terms of their relation to bone width (BW) or a derivative of BW. This argument is in keeping with the results of studies in adults that suggest that correction of BMC for bone size may be useful in evaluating bone mineralization.[2] This view is challenged by Vyhmeister and colleagues,[3] who state that the division of BMC by BW or a derivative of it (such as BW^2) may add additional errors to the estimate of bone mineralization. We suggest that although both Harkavy and Vyhmeister et al present well-developed theoretical arguments, neither position is supported by new bone mineral data.

Although no absolute method has been identified as the ideal measure by which to determine bone mineralization in infants, the relative utility of different measures of bone mineralization may be established by comparing them with independent indicators of mineral status. Both serum phosphorus and alkaline phosphatase activity are measures of mineral status in infants.[4,5] Recently, we published bone mineral indicators obtained between ten and 25 weeks postnatally in very-low-birth-weight infants.[6] Linear correlations among the biochemical indicators and BMC, BMC/BW, and BMC/BW^2 from that study (Table) demonstrate differences in relationships among serum biochemical markers and various calculations of bone mineralization.

Correlations Among BMC, BMC/BW, and BMC/BW^2 and Serum Phosphorus and Alkaline Phosphatase Activity*

Calculation of Bone Mineralization	*r*			
	Serum Phosphorus		Alkaline Phosphatase Activity	
	16 wk	25 wk	16 wk	25 wk
BMC, mg/cm	.48†	.52†	−.43	−.63‡
BMC/BW, mg/cm²	.63‡	.60†	−.57‡	−.72‡
BMC/BW² mg/cm³	.66‡	.44	−.60‡	−.56†

*BMC indicates bone mineral content; BW, bone width. The total number of patients was 20 at 16 weeks and 17 at 25 weeks.
†$P<.05$.
‡$P<.01$.

When the differences at 16 weeks are analyzed by multiple regression analyses, BMC/BW significantly increased the degree to which serum phosphorus could be predicted by BMC (R^2 increased from 23% to 48%, $P<.02$). At that age, BMC/BW increased the predictability of serum alkaline phosphatase by BMC (R^2 increased from 19% to 39%, $P<.04$). Similar relationships were noted using BMC/BW^2 instead of BMC/BW.

The association between serum biochemical measures and bone mineralization indexes obtained by single photon absorptiometry suggests that benefit may be derived by reporting BMC/BW or BMC/BW^2 as well as BMC in studies of bone mineralization in infants. These relationships must be considered, however, in the context of evidence in infants and immature animals that suggests that although serum biochemical indexes are useful, they are not highly accurate predictors of bone mineral status.[5,7]

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1. Harkavy K: Decreased bone mineral content = rickets: A misleading equation. *AJDC* 1988;142:479-480.
2. Nielsen HE, Mosekilde L, Mosekilde L, et al: Relations of bone mineral content, ash weight and bone mass: Implication for correction of bone mineral content for bone size. *Clin Orthop* 1980;153:241-247.
3. Vyhmeister NR, Linkhart TA, Christensen RA: Decreased bone mineral content = rickets: A misleading equation. *AJDC* 1988;142:480.
4. Hillman LS, Hoff N, Salmons S, et al: Mineral homeostasis in very premature infants: Serial evaluation of serum 25-hydroxyvitamin D, serum minerals, and bone mineralization. *J Pediatr* 1985;106:970-980.
5. James JR, Congdon PJ, Truscott J, et al: Osteopenia of prematurity. *Arch Dis Child* 1986;61:871-876.
6. Abrams SA, Schanler RJ, Garza C: Bone mineralization in former very low birth weight infants fed either human milk or commercial formula. *J Pediatr* 1988;112:956-960.
7. Abrams SA, Schanler RJ, Sheng HP, et al: Peripheral bone mineral content is correlated to total body calcium/serum indices of mineral status in miniature piglets. *Pediatr Res* 1988;23:297A.

In Reply.—I thank Dr Abrams and colleagues for bringing to my attention past and recent data regarding measurements of bone mineral and the choice of BMC or BMC/BW, in which BMC is the bone mineral content of scanned bone and BW is the width of the bone at the scan site. A recent symposium[1] addressed the controversy over the relative importance of BMC and BMC/BW. While BMC may be written as milligrams per centimeter, BMC is in reality an expression of bone mineral (ash) in milligrams per square centimeter, since the measurement beam has a defined width and the scan is corrected by the absorptiometer for scan length. Also, BMC/BW is an estimate of density (g/cm^3), in which BW is assumed to represent the diameter of the bone not only along the scan path but also along the beam path (ie, from radiation source to detector). As I implied in my discussion, any variation from a cylindrical shape or change in the ratio of cortex to marrow thickness would alter the ability of change in BMC/BW to represent change in bone density. However, Nielsen et al concluded that the square of the width of the radius and ulna was an excellent (and perhaps better) predictor of total cross-sectional bone area.

In reviewing animal and human data, it is clear that BMC and BMC/BW measure different aspects of calcium and bone metabolism. Clearly, BMC and BMC/BW are intimately related to one another, since 99% of body calcium is located in the skeleton, and the available calcium determines both bone growth and bone density.[2] In measurement along a single bone, BMC/BW varies less than does BMC,[3] although BMC/BW (ash content in g/cm^2) varies between bones in the same subject. Clearly, a single measurement in a single site only approximates what is happening throughout the body. Technology may allow total body BMC measurements in the near future.[4]

I am unaware of studies that relate BMC and BMC/BW values to histologic evidence of rickets. Until then, it seems more appropriate to examine three measures: (1) BMC as an estimate of body calcium accretion, (2) BW for increase in bone dimensions, and (3) BMC/BW as an estimate of bone density.

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1. Filer LJ (ed): Assessment of bone mineralization in infants. *J Pediatr* 1988;112:165-248.
2. Forbes GB: Some remarks on bone mineralization. *J Pediatr* 1988;112:167-171.
3. Vyhmeister NR, Linkhart TA: Measurement of humerus and radius bone mineral content in the term and preterm infant. *J Pediatr* 1988; 112:188-195.
4. Barden HS, Mazess RB: Bone densitometry in infants. *J Pediatr* 1988;112:172-177.

In Reply.—We agree with Abrams et al that correction of BMC for BW may be useful in evaluating bone mineralization, especially for correcting cross-sectional data for differences in BW among infants of the same age. The usefulness of dividing by BW is evident in the data reported by Abrams et al. The cross-sectional population variance for radius BMC/BW was less than that for BMC, which suggests that BMC/BW might allow the detection of statistically significant differences between smaller groups of infants than would be possible using BMC. This advantage disappears, however, if the variance for BW is high, as in our studies of humerus BMC using the Norland 278A densitometer. The relatively poor reproducibility of BW measurements in our study prevented any potential improvement that might be gained by using BMC/BW instead of BW as an assessment of bone mineral status. The reproducibility of BW data may have been better in the study by Abrams et al, although one cannot assert this from their data, because neither BW reproducibility nor the method for determining reproducibility were reported.

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In Other AMA Journals

JAMA

Impact of a Medical Journal Club on House-staff Reading Habits, Knowledge, and Critical Appraisal Skills

M. Linzer; J. T. Brown; L. M. Frazier; E. R. DeLong; W. C. Siegel (*JAMA* 1988; 260:2537)

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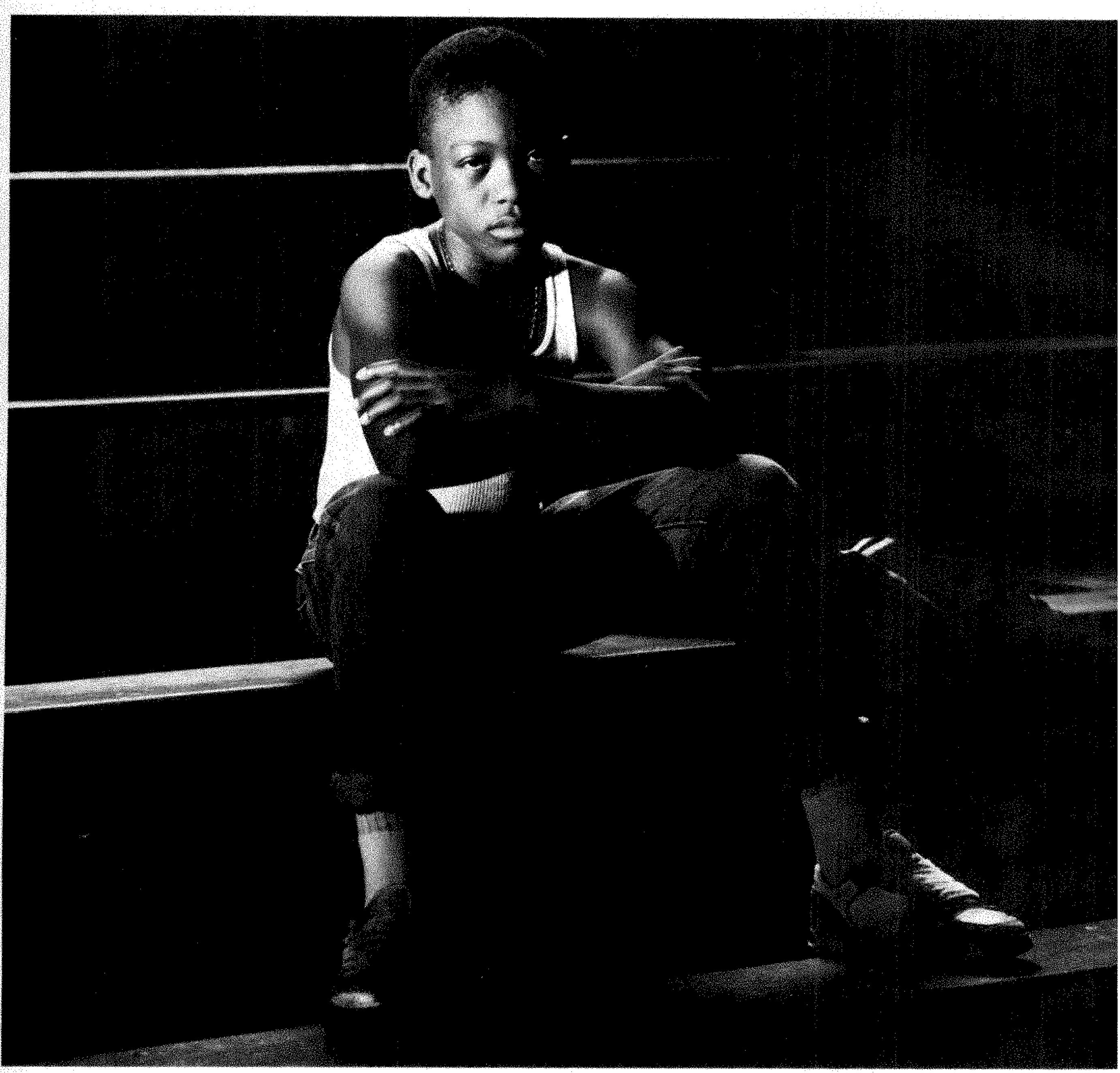

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Progress Toward Achieving the National 1990 Objectives for Immunization

THE 1990 health objectives for the nation included 18 objectives on immunization.[1] This update reports on progress toward achievement of these objectives through 1987.

IMPROVED HEALTH STATUS

The first eight objectives cite the morbidity reduction targeted for eight diseases by 1990.

The targets for diphtheria and poliomyelitis appear to have been met, and substantial progress toward the targets for tetanus, rubella, and congenital rubella syndrome has been achieved. Morbidity from mumps had been declining until 1986, when the incidence of mumps increased 161%.[2] The 12,848 cases reported in 1987 are the most since 1979. This increase largely reflected outbreaks in high schools and colleges and probably resulted from the absence or lack of enforcement of school immunization requirements in some states.[2-4] Illinois and Tennessee had the highest mumps incidence rates in 1986 and 1987; these two states began enforcing comprehensive school laws requiring mumps vaccination in September 1987 and September 1988, respectively. During the first 26 weeks of 1988, 2945 cases were reported in the United States, representing a 69% decrease from the same period in 1987.

Between 1981 and 1987, the number of reported measles cases stabilized, with slightly more than 3000 average annual cases (range: 1497 cases in 1983 to 6282 cases in 1986). Outbreaks have occurred among both preschool-aged children, many of whom were unvaccinated, and high school- and college-aged persons, many of whom had been vaccinated. In many recent outbreaks, persons who received measles vaccine at 12-14 months of age have been at higher risk for measles than those vaccinated at greater than or equal to 15 months of age.[5] Intervention strategies to eliminate measles continue to be evaluated.[6]

Improved surveillance indicates that pertussis also occurs in adolescents and adults as well as in infants and young children, although the illness is milder in these older persons.[7] Increases in reported cases in 1985 and 1986 may be due to improved diagnosis and surveillance since diphtheria-tetanus-pertussis vaccine coverage in children does not appear to have declined.

IMPROVED SERVICES AND PROTECTION

By 1990, at least 90% of all children by age 2 should have completed their immunization series—measles, mumps, rubella, polio, diphtheria, pertussis, and tetanus.

Although evaluation of progress toward this objective is difficult because of limited base-line data, it appears likely that this objective will not be met. In 1979, an estimated 70%-80% of 2-year-old children had received their basic immunization series. In the most recent U.S. Immunization Survey in 1985, 77% of 2-year-olds whose parents had records at home had received their basic series. Recent outbreaks of measles among unimmunized preschoolers also have shown that inadequate immunization levels still occur. To ensure that infants begin and complete their immunization series on schedule, efforts to develop recall and outreach systems must be continued.

By 1990, at least 95% of children attending licensed day-care facilities and kindergarten through 12th grade should be fully immunized.

Although national data are not available for children beyond the first grade, extrapolation of school entry data since 1980 suggests that this objective will be met. For the 1986-87 school year, immunization levels in licensed day-care facilities exceeded 90%. Of children entering kindergarten or first grade, 97% had been immunized.

By 1990, at least 60% of high-risk populations, as defined by the Immunization Practices Advisory Committee (ACIP) of the Public Health Service, should be receiving annual immunization against influenza.

This objective is unlikely to be met unless efforts are substantially intensified. The 1985 U.S. Immunization Survey indicates that only approximately 20% of high-risk persons received influenza vaccine during the preceding year.

INCREASED PUBLIC AND PROFESSIONAL AWARENESS

By 1990, all mothers of newborns should receive instruction on immunization schedules for their babies before leaving the hospital or after home births.

This objective will probably be met because substantial progress has been made in educating mothers of newborns about immunizations. As of 1986, 39 of 52 jurisdictions (50 states, the District of Columbia, and New York City) had hospital-based maternal education programs in at least 90% of targeted hospitals.

IMPROVED SURVEILLANCE AND EVALUATION

By 1990, at least 95% of all children 18 years of age and under should have up-to-date official immunization records in a uniform format using common guidelines for completion of immunization.

Standardized immunization records are now available in all states. Given the likelihood of achieving immunization level targets, this objective probably will be met. Although all states recommend the same immunization series, school immunization requirements vary from state to state. Consequently, the definition of "complete series" may vary.

By 1990, surveillance systems should be sufficiently improved that (1) at least 90% of those hospitalized and 50% of those not hospitalized with vaccine-preventable diseases of childhood are reported and (2) uniform case definitions are used nationwide.

Meeting the target for hospitalized persons may be feasible, but it is less likely that the target for persons who are not hospitalized can be met. The completeness of reporting varies by disease. Most cases of poliomyelitis, tetanus, and diphtheria are probably diagnosed, and nearly all are reported. As a result of the measles elimination initiative, measles reporting is now considered to be nearly complete. However, because of the variability in clinical manifestations of rubella, mumps, and pertussis, reporting of these diseases is probably incomplete. An estimated 22% of confirmed and compatible cases of congenital rubella syndrome diagnosed during the neonatal period are reported.[8]

Uniform case definitions exist for measles, mumps, rubella, congenital rubella syndrome, poliomyelitis, diphtheria, tetanus, pertussis, and Haemophilus influenzae type b.

By 1990, at least 60% of high-risk populations, as defined by the ACIP, should have received vaccination against pneumococcal pneumonia.

The 1985 U.S. Immunization Survey indicates that approximately 10% of high-risk persons had received pneumococcal polysaccharide vaccine. Although administration of this vaccine is reimbursed under Medicare, this objective is unlikely to be met.

By 1990, at least 50% of people in populations designated as targets by the ACIP should be immunized within 5 years of licensure of new vaccines for routine clinical use.

Recently licensed vaccines include hepatitis B vaccine (licensed in 1982), Haemophilus influenzae type b polysaccharide vaccine (HbPV, licensed in 1985), and Haemophilus influenzae type b conjugate vaccine (HbCV, licensed in 1987). Hepatitis B vaccine is recommended for persons who are at risk of contact with blood or blood products (primarily health-care workers), homosexual men, household contacts of carriers of hepatitis B surface antigen, and users of illicit injectable drugs. Since data suggest that coverage for high-risk groups varies from 2% to 50%, this objective may be met in some target groups. HbCV is recommended for all children at 18 months of age and will likely replace most use of HbPV in 1988. Evaluating progress toward the objective for HbCV is not possible because of a lack of national data concerning coverage with this vaccine.

By 1990, no comprehensive health insurance policies should exclude immunizations.

Comprehensive data about insurance coverage of immunizations are not available. However, approximately 20 million persons are receiving services from health maintenance organizations that provide both preventive and treatment services. Medicaid provides reimbursement for childhood vaccine and Medicare provides reimbursement for pneumococcal polysaccharide vaccine. In 1987, Congress authorized the Health Care Financing Administration to conduct a cost-effectiveness study beginning during the 1988-89 influenza season to determine whether influenza vaccine should be covered under Medicare.

By 1985, the nation should have a plan in place to mount mass immunization programs in the face of possible epidemics of influenza or other epidemic diseases for which vaccines may exist.

This objective has been met.

Reported by: Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Public Health Svc. Center for Biologics Evaluation and Review, Food and Drug Administration. Microbiology and Infectious Diseases Program, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Div of Viral Diseases and Div of Bacterial Diseases, Center for Infectious Diseases; Div of Immunization, Center for Prevention Svcs, CDC. (MMWR vol 37, No. 39)

CDC Editorial Note: Overall progress toward the 1990 objectives relating to childhood vaccines is encouraging, although full immunization of children at the earliest appropriate age has not yet been assured. Of greater concern is the relative lack of progress toward the objectives relating to vaccines used primarily for adults. Improving immunization coverage for adults is difficult because regular immunization is not traditional among this age group and because target groups vary for different vaccines. In January 1985 and April 1987, CDC convened adult immunization community forums to discuss development and implementation of programs to ensure appropriate immunization of adults. These forums led to the formation of the National Coalition for Adult Immunization to pomote adult immunizations. This coalition represents voluntary organizations, professional physician groups, and manufacturers of vaccines.

As a result of an internal assessment by the National Institute of Allergy and Infectious Diseases and a priority-setting study by the Institute of Medicine,[9] priority has been placed on the rapid development of several new vaccines. Introduction of any of these new vaccines would pose additional challenges in achieving the target of 50% coverage in designated target groups within 5 years of licensure.

Although efforts to reduce mumps, measles, and pertussis must be continued, improved surveillance of these and other infectious diseases will allow for more accurate assessment of future efforts toward prevention of these diseases. In addition, increased educational efforts that stress the importance of childhood and adult immunizations will assure future strides in reduction of vaccine-preventable diseases.

References

1. Public Health Service. Promoting health/preventing disease: objectives for the nation. Washington, DC: US Department of Health and Human Services, Public Health Service, 1980;21-4.
2. CDC. Mumps—United States, 1985-1986. MMWR 1987;36:151-5.
3. CDC. Mumps outbreaks on university campuses—Illinois, Wisconsin, South Dakota. MMWR 1987;36:496-8,503-5.
4. Cochi SL, Preblud SR, Orenstein WA. Perspectives on the relative resurgence of mumps in the United States. Am J Dis Child 1988;142:499-507.
5. Orenstein WA, Markowitz LE, Preblud SR, Hinman AR, Tomasi A, Bart KJ. Appropriate age for measles vaccination in the United States. Dev Biol Stand 1986;65:13-21.
6. CDC. Measles—United States, first 26 weeks, 1987. MMWR 1988;37:53-7.
7. CDC. Pertussis surveillance—United States, 1984 and 1985. MMWR 1987;36:168-71.
8. Cochi SL, Edmonds LD, Dyer K, et al. Congenital rubella syndrome in the United States, 1970-1985: on the verge of elimination. Am J Epidemiol (in press).
9. Hinman AR. Vaccine development and utilization: symposium summary. Rev Infect Dis (in press).

Nonsteroidal Anti-inflammatory Drugs in Pediatric Patients

In this issue of *AJDC*, Olson et al[1] offer preliminary evidence for the value of nonsteroidal anti-inflammatory drugs (NSAIDs) as an adjunct in the treatment of chronic iridocylitis in childhood. This is a vexingly difficult therapeutic problem, usually occurring in patients with juvenile rheumatoid arthritis (JRA). The only systemic agents heretofore effective are corticosteroid or immunosuppressive drugs. Although the study of Olson et al is a retrospective review of 14 patients, two types of evidence are offered to suggest a therapeutic benefit: (1) a decreased need for systemic or topical steroids and (2) reduction of inflammatory cells in the anterior chamber of the eye as estimated by slit-lamp examination. It was the impression of the authors that all 14 patients improved after NSAIDs were added to the regimen (I have a similar impression in two patients with uveitis in our own clinic). They point out that their patients had been under observation for several months before the initial administration of NSAIDs so that the effect of the drug was compared with a prolonged baseline period without NSAID therapy.

See also p 1289.

Nevertheless, one must remember that patients with uveitis do improve with systemic and local steroids and that proof of therapeutic efficacy will only come from a controlled prospective study. It is, however, this kind of clinical experience that should stimulate the design and implementation of a prospective study. This could logically be done by the Pediatric Rheumatology Collaborative Study Group, a multicentered consortium that has conducted many important clinical trials in JRA.[2-6]

The article by Olson et al allows me to emphasize several points about the management of JRA.

The first is the common occurrence of uveitis in patients with JRA, particularly in monoarticular or pauciarticular JRA.[7,8] Because this form of JRA is common, often mild, frequently misdiagnosed, and very responsive to treatment (even without a diagnosis!), the concomitant occurrence of chronic uveitis is often missed, resulting in refractory uveitis and/or loss of vision. Thus, slit-lamp examinations must be done for all children with JRA, at six-month intervals; in patients with active pauciarticular JRA, these should be done at four-month intervals, especially during the first years of the disease. This will permit early diagnosis and treatment.

The presence of a positive antinuclear antibody (ANA) test is also a valuable correlate of uveitis. Glass et al[7] reported that 15 (63%) of 24 patients with JRA with uveitis had ANA positivity; patients with monoarticular JRA without uveitis had an incidence of ANA positivity of 28.5% (6/21). Glass et al also noted the association of uveitis with the HLA-Bw4. Thus, all patients with positive ANA tests need ophthalmic consultation.

The final point the article by Olson et al highlights is the value of NSAIDs in the treatment of JRA. Two NSAIDs are approved for children over the age of 2 years—tolmetin sodium (Tolectin) (available as 200-mg scored tablets and 400-mg capsules [McNeilab Inc, Spring House, Pa]) and naproxen (Naprosyn) (available as 250-, 375-, and 500-mg tablets and 125 mg/5 mL suspension [Syntex Laboratories Inc, Palo Alto, Calif]). Both are safe and effective, better tolerated, and easier to use than high-dose aspirin therapy.[2,9]

I believe NSAIDs are the initial treatment of choice for most patients with JRA. There is some risk of Reye's syndrome with high-dose aspirin therapy. Most patients receiving high-dose aspirin therapy find it an ordeal (13 aspirins a day for a 40-kg child)—even if their stomach tolerates it. Salicylate and transaminase levels must be closely monitored while the patient is receiving aspirin therapy. Indeed, the need to discontinue therapy is greater with aspirin than with the NSAIDs.[2,9] Nevertheless, aspirin is still listed as the treatment of choice by current pediatric, rheumatology, and immunology textbooks (including my own).[10] I disagree.

As stated, tolmetin (20 to 30 mg/kg/d in four divided doses) and naproxen (10 to 15 mg/kg/d in two divided doses) are the only two NSAIDs approved for children. Indomethacin, as used by Olson et al, is also available, but data on safety in children under age 15 years are lacking. Fatal reactions have been recorded.[11] It is a rare patient who is unresponsive to tolmetin, naproxen, and aspirin who will respond satisfactorily to indomethacin. Other NSAIDs (ibuprofen, fenoprofen, ketoprofen, proquazone, meclofenamate) have also been studied in children,[2-12] but are not yet approved for use. They are best avoided.

In sum, NSAIDs for children have come of age. They are the initial treatment of choice for JRA because of their safety, effectiveness, and ease of administration, and, as Olson et al indicate, they may also be of value in the management of chronic iridocyclitis.

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References

1. Olson NY, Lindsley CB, Godfrey WA: Nonsteroidal anti-inflammatory drug therapy in chronic childhood iridocyclitis. *AJDC* 1988;142:1289-1292.

2. Levinson JE, Baum J, Brewer E Jr, et al: Comparison of tolmetin sodium and aspirin in the

treatment of juvenile rheumatoid arthritis. *J Pediatr* 1977;91:799-804.

3. Brewer EJ, Giannini EH, Baum J, et al: Aspirin and fenoprofen (Nalfon) in the treatment of juvenile rheumatoid arthritis: Results of the double-blind trial. *J Rheumatol* 1982;9:123-128.

4. Brewer EJ, Giannini EH, Baum J, et al: Ketoprofen (Orudis) in the treatment of juvenile rheumatoid arthritis. *J Rheumatol* 1982;9:144-148.

5. Brewer EJ, Giannini EH, Baum J, et al: Sodium meclofenamate (Meclomen) in the treatment of juvenile rheumatoid arthritis. *J Rheumatol* 1982;9:129-134.

6. Brewer EJ, Giannini EH, Baum J, et al: Proquazone (Biarsan) in the treatment of juvenile rheumatoid arthritis. *J Rheumatol* 1982;9:135-139.

7. Glass D, Litvin D, Wallace K, et al: Early-onset pauciarticular juvenile rheumatoid arthritis associated with human leukocyte antigen DRw5, iritis, and antinuclear antibody. *J Clin Invest* 1980;66:426-429.

8. Schaller J, Kupfer C, Wedgwood RJ: Iridocyclitis in juvenile rheumatoid arthritis. *Pediatrics* 1969;44:92-100.

9. Makela AL: Naproxen in the treatment of juvenile rheumatoid arthritis. *Scand J Rheumatol* 1977;6:193-205.

10. Schaller JG Szer I: Rheumatic Disorders, in Stiehm ER (ed): *Immunologic Disorders in Infants and Children*, ed 3. Philadelphia, WB Saunders Co, 1989, pp 542-580.

11. Jacobs JC: Sudden death in arthritic children receiving large doses of indomethacin. *JAMA* 1967;199:932-934.

12. Calin A, Bennett RM, Sukhupunyaraksa S, et al: Double-blind, multi-centre parallel trial of ketoprofen and ibuprofen in the treatment of rheumatoid arthritis. *J Rheumatol* 1977;4:153-157.

Book Review

Hearing Impairment in Children, edited by Fred Bess, 467 pp, with illus, $55, Parkton, Md, York Press, 1988.

Hearing Impairment in Children represents the proceedings of the Third International Symposium on Childhood Deafness. The symposium, which was held in Nashville, Tenn, in July 1986, was designed to bring together recognized authorities in a wide variety of disciplines and to update our understanding of the issues related to childhood hearing impairment. While the book comes out nearly two years after the symposium was held, the time was well spent. The editing of the book is superb, and the long interval has not diminished the importance of the material.

The number and complexity of issues that either touch on or are touched by childhood hearing impairment are striking. There seems to be no area of human science or medicine that does not in some way play a role in the cause, diagnosis, or treatment of hearing impairment.

The book is divided into three sections: (1) "Issues on Etiology/Auditory Disorders," (2) "Issues on Identification and Assessment," and (3) "Issues on Management." Overall, the chapters in each section are clear, concise, and informative. Differential diagnosis (Glasscock et al), infectious agents (Bergstrom), otitis media (Giebink), and other topics in the first section are dealt with in terms that are suitable for unsophisticated readers as well as for those with more in-depth knowledge. The chapter on the increasing role of geneticists in the management of hearing impairment (Shaver) is an especially enlightening contribution. In addition, Shaver's insights into the importance of proper genetic counseling, especially with respect to the attention that must be given to cultural differences between deaf and hearing families, are important for all to consider.

In the second section, the biases of the contributing authors are more apparent to me, but they do not detract from the meaningfulness of the reports. Most major points regarding the level of sophistication of our identification and assessment tools (such as screening with the auditory brain-stem response [Weber], behavioral testing [Diefendorf], diagnosis with auditory evoked potentials [Schwartz and Costello], and immittance [impedance and admittance measures] testing [Northern]) are appropriately balanced by discussions of their limitations. Matkin, as usual, provides important insights in his thoughtful chapter on the changing demographics of hearing impairment in children and the approach that is taken by health care professionals for identifying hearing loss. His appeal for a better understanding of hearing impairment in children should be read by all primary care physicians. In addition, Ross and Seewald discuss their sensible approach to fitting hearing aids on children, and Kretschmer and Kretschmer share their interesting perspective on communication and language assessment.

The long final section reflects a shift in emphasis in recent years from methods of identification and assessment to means of managing the hearing-impaired child. Chapters are devoted to amplification (Hawkins, and Rintelmann and Bess), tactual aids (Oller and Eilers), cochlear implants (Johnson), otitis media (Feagans et al), speech and language development (Levitt and McGarr), management (Moeller, Davis), and, finally, the needs of families and the attitudes of professionals toward them (Maliszewski, Knox). A consistent theme is that hearing-impaired children will have difficulty in speech, language, and social development unless innovative and aggressive approaches to management are initiated early and followed up consistently. The problems associated with the proper management of children with hearing impairment are many, but it is clear from this section that work is now being done that holds promise for increasing the ability of hearing-impaired children to develop, learn, and function in our society.

This book summarizes a wealth of information in a readable fashion. It is long and has been written by a great number of authors, with unavoidable differences in approach and style, but it overcomes those drawbacks easily. There is something in this book for anyone who is interested in any aspect of the problem of hearing impairment in children. The reference lists in each chapter are sufficient to direct interested readers to primary research reports or other review materials. The book presents a fine review of the current state of affairs with respect to hearing impairment in children and should become a valuable resource for professionals in a variety of disciplines.

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The Editorial Board Speaks . . .

E. Richard Stiehm, MD

Dr E. Richard Stiehm is one of our newest Editorial Board members. My association with Dick goes back to internship; we both served at the now defunct Philadelphia General Hospital and have been colleagues ever since. We edited two editions of the text *Immunologic Disorders in Infants and Children*, and Dick alone has now edited the third edition, due out in the fall of 1988.

He received his MD degree from the University of Wisconsin, was a postdoctoral fellow in biochemistry at Wisconsin, and then completed a pediatric residency at Columbia-Presbyterian College of Medicine, New York, and a fellowship in immunology/hematology at the University of California, San Francisco. He has been a faculty member at Wisconsin and at UCLA, where he is now professor.

Dick has a distinguished academic career with more than 150 publications, many of which are seminal in pediatric immunology. He is a superb teacher and clinician and is nationally and internationally recognized for his contributions to the field of immunology.

He is married to Judith Hicks Stiehm, and they have three children, Jamie, Carrie, and Meredith. Judith is provost of Florida International University, and Dick will be on sabbatical leave at Miami University in 1989.

SOME OF MY BEST CLINICAL PEDIATRICIANS ARE RESEARCHERS

We all know a few: a busy, full-time practicing pediatrician who somehow manages to publish case reports, review articles, write chapters, conduct office-based drug trials, submit editorials, etc. My colleagues, Sheldon Siegel and Gary Rachelefsky, come to mind. These dynamos truly bridge the gap between academic medicine and practice, and seem to love it. They are usually the most respected clinicians in the community. Their contributions are immense. We need more of them.

One common ingredient among these physicians, I believe, is a background in research—in undergraduate school, medical school, residency, or fellowship. Somewhere in their medical education, they learned to observe, record, and write.

Research training for the medical trainee is like music lessons for the 5-year-old child. The discipline is good for you, it will make music part of your life, and it will make musicians of a few of you. Like music lessons, few choose to try research, but all who do profit from it, and hardly any regret the hours spent at the bench—piano or research. Many practicing pediatricians, I have noticed, reminisce fondly about the time in the research laboratory.

Why don't more students or residents try research? The answers include the following: (1) "I don't know how to do research," (2) "I'm afraid to apply," (3) "I probably won't get accepted," (4) "I'm too busy," (5) "I'll neglect my other work," (6) "I could be earning more money doing something else," (7) "It's not really medicine," and (8) "I'll have to work late at night." These reasons are similar to the reasons why teenage boys are afraid to call for that first date: (1) "I'm afraid to call her," (2) "She'll probably say *no*," (3) "I've never gone with a girl before," (4) "I don't know what to talk about," and (5) "I don't know how to dance very well," or his parents' objections to dating: (6) "You're too busy," (7) "You'll neglect your schoolwork," (8) "You'll spend all your hard-earned money," (9) "She doesn't go to our church," or (10) "You'll have to drive at night." Well, boys (and nowadays, girls) do make that first telephone call and students do research. And both learn enormously. Some of what they learn is listed in the Table. Research training is the music lessons of medical progress: learning to make and share observations throughout a lifetime in medicine.

What Researchers Learn (in Addition to What They Are Researching)

1. Value of careful and controlled observations (The untreated mouse survived too!)
2. Importance of special knowledge (How do I turn on this computer?)
3. Acquisition of new skills (Neonatal thymectomy is harder than an appendectomy!)
4. Utilizing skills of associates (Mr Williams will show you how to measure the pH of the buffer)
5. Go new places (I have never been in a bathhouse before!)
6. Conquer new situations (I have to present a paper at the APS/SPR!)
7. Value of persistence (But this is in the fourth revision!)
8. Learn about yourself (I actually like to do postmortems!)
9. Importance of modern technology (The manuscript you lost is still in the word processor!)
10. Value of good writing (We like your data, but please translate into standard English!)

If research is so good, why is it not part of the medical school or pediatric residency? It's much like music in the public schools. It's costly, it's not core, and it's not demanded by the residents. Yet I believe that each pediatric residency (and medical school) should require a paper, a case study, a chart review and analysis, or a review of some important pediatric problem (eg, homeless children). This may require a period in a research laboratory; thus, elective time must be provided. All would be presented at grand rounds or faculty research seminar, and most would be published. Many outstanding undergraduate schools (Princeton and Swarthmore) require a senior thesis; my medical school (Wisconsin) used to require one. One pediatric residency program (Children's Hospital of Philadelphia) is implementing such a requirement. The students accepted it, complained a little bit, and profited immensely. It teaches critical thinking, accurate reporting, and clear exposition. Yogi Berra once said, "It's amazing what you can observe by just looking."

Thus, my message for medical students and residents: Try research, it's always educational, usually enjoyable, and sometimes sensational. You may not discover the cure for acquired immunodeficiency syndrome, but you will become a better physician!

Special Contribution

Helping Families Get Through the Holidays After the Death of a Child

Abby L. Wasserman, MD

The Thanksgiving turkey is about to be carved when the mother starts crying. On the way home, after the Thanksgiving dinner, the parents wonder how they are ever going to make it through Christmas or Hanukkah and the New Year. They are grieving for the child who died this past year, and the family traditions of the holiday season just accentuate the pain and emptiness left by the loss of their child.

Holidays and anniversaries of significant dates for the family (eg, the child's birthday, christening, confirmation, etc) are especially difficult times for the surviving family members.[1] It is at these times that the child's absence is especially marked. The first year is the hardest; during each subsequent year, it gets a little easier for the family to handle the holidays. They must learn to take one day at a time. The anticipation of the holiday/anniversary is actually worse than the day itself.

Conflicts between the parents may arise because they are grieving differently from each other. Perhaps the mother is withdrawn, tearful, and just sits and stares into space, whereas the father is away from the home working late into the night, trying to forget his loss. The father may be feeling good one day but feel impotent since he cannot cheer up his wife; whereas on another day she may feel that things are improving, and he cannot get through the day. They become distant from each other, and when they are together, they are unable to talk, especially about the loss that has so affected them. In addition, they are probably each feeling guilty[2] because they feel responsible for their child's death,[3] whether this is based on fact or not. They may also be blaming each other.[4] They need help in understanding these negative but normal feelings. Open communication between family members should be encouraged. The physician can really be of service to this family by pointing out that they are both grieving, albeit in different ways, and perhaps at different rates. They may need a recommendation for outside support (counselor, group meeting, etc) because they are unable to support each other.

The surviving children also must be considered. The understanding of death is age-dependent.[5] The 3-year-old child seeing the mother crying will probably wonder what he or she did wrong to cause all the tears. The young child must be told that he or she did nothing wrong, that mother is crying because she misses (deceased child) but that she is very happy that (living child) is here for her to love and hug. The 16-year-old sibling, on the other hand, may be reacting the way one or the other parent is, and perhaps is not dealing with his or her emotional turmoil effectively. The physician is in the logical position to ask about the child and/or adolescent and to ascertain how they are doing since the death of the sibling. Sometimes the physician needs to see the child and/or adolescent, since the parent, especially one who is grieving, is unable to assess accurately the psychiatric status of the surviving siblings.[6]

Grandparents can be positive and/or negative forces.[3] They are doing their own grieving for their lost grandchild. Sometimes they can help their children; sometimes they cause more problems. If the physician sees that the grandparents (or any other friend or relative) are more a hindrance than a help, a recommendation that they should not be with the parents should be made. The parents will be relieved since they needed the separation but were unable to accomplish it.

Religious beliefs are usually a solace and help. Organized religion, regardless of the denomination, has means, usually rituals, for dealing with death. These rituals should be encouraged because they allow for support of families during the period of mourning. However, it must be remembered that children are concrete thinkers and may interpret abstract religious teachings in a way not intended. As an example, a 4-year-old boy became unmanageable after the death of his older sibling. When asked about this behavior change for the worse, he replied that he was not going to be so good that Jesus would want him. This child had been told that his brother was so wonderful that Jesus wanted him to live with him in heaven. His bad behavior was his way of saying, "I don't want to die, I don't want to leave you."

In getting through the Christmas holidays, the families have to decide what they can handle comfortably.[7] Even the question of whether to celebrate Christmas at all needs to be answered. As a family, they may decide to forego the holiday. Perhaps they will just go away on a little

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Accepted for publication Oct 12, 1988.

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vacation. However, even though the adults in the family may wish not to bother with Christmas, the younger children in the family regard Christmas as their time to get presents and to have fun; depriving them of the festivities to which they and their friends are looking forward may cause problems. The younger child is so self-centered that the absence of the sibling at the holiday celebrations has little bearing on the child's expectations of the holiday.

These families have to be told that it is all right to make changes in their celebration; in fact, changes can make things less painful (a different tree with different decorations, opening the presents at a different time, a different menu for dinner, etc). Perhaps it would be better to have the festivities at another family's home. In this way, when they return home, Christmas is over—there are no trees, decorations, wrappings, holiday food, etc, to remind them continually of the holiday. Some families feel better by helping others during the holidays. Examples include giving to charity the money they would have spent on presents for the deceased child; adopting a needy family; inviting people away from home over to celebrate; and visiting orphanages or hospitals. There is no set formula. What the family decides to do one year may not be what they decide to do the next year.

Buying presents is one of the most troublesome aspects of the holidays for people in general. Many people, usually mothers, wear themselves out trying to buy the perfect gift for each individual. After a death, this fatiguing aspect of Christmas shopping can precipitate depression or worsen existing depression. To minimize the fatigue, the following suggestions may help: to make a list ahead of time of gifts for each person; to do all the shopping in one store at one time; to use catalog shopping (all gifts can be ordered over the telephone and can arrive already wrapped); or to forego gift-giving altogether.

Another question parents frequently ask is what to do about the Christmas stockings. It is especially hard on the parents when each stocking has one family member's name on it, and they come across the one for the dead child. The family can decide to put up none of the stockings, to put up all of the stockings, to put up some and not others, to put them up in a different place, etc. The Compassionate Friends Inc[7] even suggests writing thoughts and feelings about the absent child on pieces of paper that are put into the child's stocking, perhaps to be read by the family together or by each one quietly.

Besides sharing of thoughts through use of the Christmas stocking, other families have started new traditions in memory of the departed child. Some families put a small Christmas tree on the child's grave. Others light a candle

Table 1.—Talking With Bereaved Parents*

Dos	Don'ts
DO let your genuine concern and caring show.	DON'T let your own sense of helplessness keep you from reaching out to a bereaved parent.
DO be available.	DON'T avoid them because you are uncomfortable.
DO call or write to the family if it feels right.	DON'T say you know how they feel (unless you have lost a child yourself you probably do not know how they feel).
DO say you are sorry about what happened to their child and about their pain.	DON'T say "you ought to be feeling better by now" or anything else that implies a judgment about their feelings.
DO allow them to express as much grief as they are feeling at the moment and are willing to share.	DON'T tell them what they *should* feel or do.
DO encourage them to be patient with themselves, not to expect too much of themselves, and not to impose any "shoulds" on themselves.	DON'T change the subject when they mention their dead child.
DO allow them to talk about the child they have lost as much and as often as they want to.	DON'T avoid mentioning the child's name.
DO talk about the special, endearing qualities of the child they have lost.	DON'T try to find something positive (eg, a moral lesson, closer family ties, etc) about the child's death.
DO give attention to the surviving siblings.	DON'T point out that at least they have their other children.
DO reassure them that they did everything that they could.	DON'T say that they can always have another child.
DO share your personal experiences of death and grieving if it seems useful and normal.	DON'T suggest that they should be grateful for their other children.

*Modified with permission from copyrighted material by Lee Schmidt, RN, MN, Parent Bereavement Outreach, Santa Monica, CA 90402.

Table 2.—Support Groups for Parents Who Have Lost a Child

For parents with children with cancer

Candlelighters
Childhood Cancer Foundation, Suite 1001
1901 Pennsylvania Ave NW
Washington, DC 20006
(202) 659-5136

For parents who have lost a child for any reason

Compassionate Friends US Headquarters
PO Box 3696
Oakbrook, IL 60522-3696
(312) 990-0010

For parents who have lost a child through sudden infant death syndrome

National SIDS Foundation
8200 Professional Place, Suite 104
Landover, MD 20785
(800) 212-7436

For parents who have had a miscarriage, stillbirth, or neonatal death

Source of Help in Airing and Resolving Experiences (SHARE)
St Elizabeth Hospital
211 South Third St
Belleville, IL 62222
(618) 234-2415

Information referral service for self-help groups in the United States

National Self-Help Referral Center
1600 Dodge Ave, Suite S-122
Evanston, IL 60201
(312) 328-0470 (10 AM to 5 PM)

or order special plants or flowers as a memorial for their child. Parents have to be told that it is fine if they wish to memorialize their child through these means since some people may want an external reminder of their child but feel that others may think it frivolous, thereby depriving themselves of this source of comfort.

Families in mourning have to be told that it is all right to have fun. Laughter is the best medicine for helping the bereaved cope with their loss. Having a good time does not mean that the parents loved their child any less; in fact, they may be showing more love because by enjoying themselves, they are bringing their family closer together.

In talking with bereaved parents at any time, not only during the holiday season, there are specific ways one can help the conversation flow, especially by staying away from expressions that bereaved parents resent. A list of "dos" and "don'ts" in talking with bereaved parents is given in Table 1. As far as the "don'ts" are concerned, if the parents bring up any of these points, the physician has to use his or her own judgment as to whether to agree or not. For example, even though it is not good for the professional to find something positive in the child's death because some parents may get very angry, if the parent says, "Well, at least someone else is living because of our child's heart," it is in everyone's interest to agree and support the family in their outlook. However, if the mother states that she wants to get pregnant right away, it behooves the physician to discuss with her her feelings of emptiness and loss for the dead child, but to point out also that the new baby cannot and *should* not replace the dead child.[4] If these feelings are not resolved prior to the birth of another child, there is a high likelihood of future psychological problems between the parent and the child.

Besides the support the physician can offer to the family, getting to know other parents who have lost children through death is very helpful. Listed in Table 2 are some of the better-known parent support groups.

The holidays and anniversary dates are very difficult for families who have lost a child, but with supportive and caring people to help them, each year *will* get a little easier.

References

1. Krupnick JL: Bereavement during childhood and adolescence, in Osterweis M, Solomon F, Green M (eds): *Bereavement: Reactions, Consequences, and Care.* Washington, DC, National Academy Press, 1984, p 132.

2. Kubler-Ross E: *On Death and Dying.* New York, Macmillan Publishing Co Inc, 1969, pp 142-143.

3. Johnson J, Johnson SM: *Children Die, Too.* Council Bluffs, Iowa, Centering Corp, 1979, pp 7-10.

4. Gonda TA, Ruark JE: *Dying Dignified: The Health Professional's Guide to Care.* Menlo Park, Calif, Addison-Wesley Publishing Co, 1984, pp 187-188.

5. Lewis M: *Clinical Aspects of Child Development: An Introductory Synthesis of Developmental Concepts and Clinical Experience.* Philadelphia, Lea & Febiger, 1982, pp 324-341.

6. Angold A, Weissman MM, John K, et al: Parent and child reports of depressive symptoms in children at low- and high-risk of depression. *J Child Psychol Psychiatry* 1987;28:901-915.

7. The Compassionate Friends Inc: *Getting Through the Holidays.* Aurora, Ill, Fox Valley Chapter of the Compassionate Friends Inc, 1980.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Malignant Peritoneal Mesothelioma in Childhood

Gordon R. Armstrong, BMedSci, BM, BS; Faro Raafat, MD, MRCPath; Lewis Ingram, MRCP; Jillian R. Mann, MB, FRCP (*Arch Pathol Lab Med* 1988;112:1159-1162)

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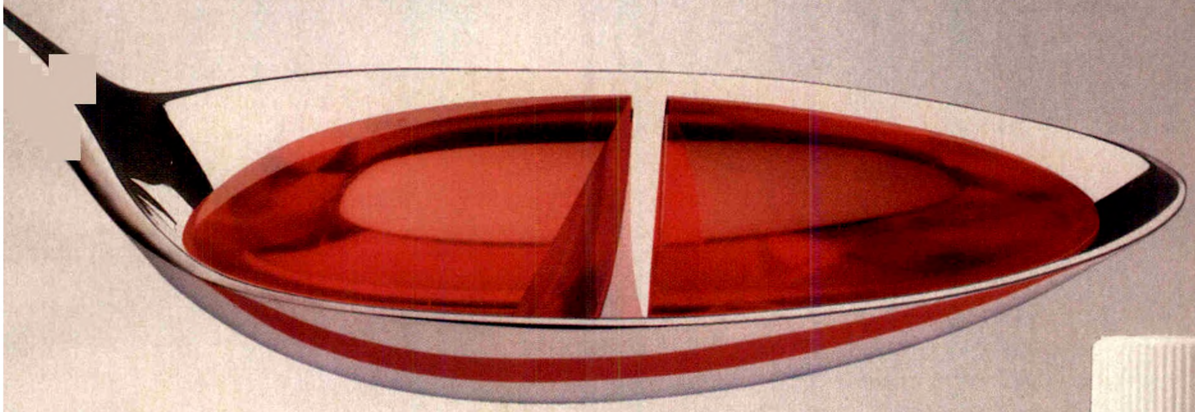

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REFERENCES

1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986; pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharm Times* 1985;51(1):80-90.

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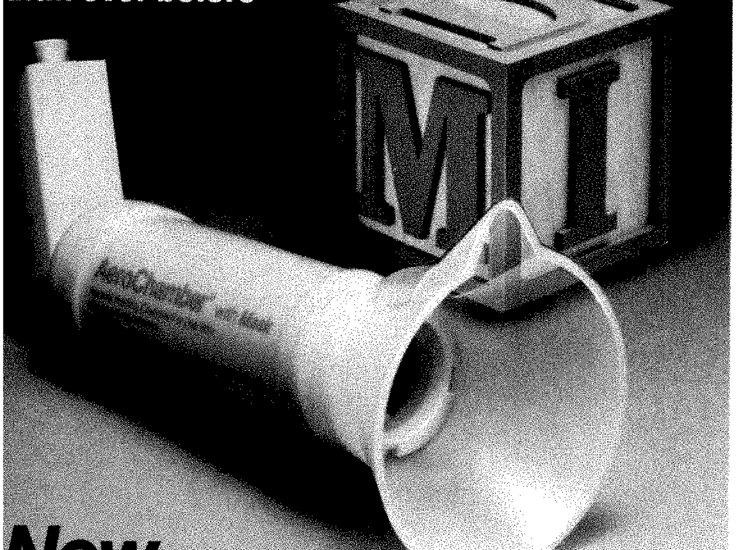

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Nonsteroidal Anti-inflammatory Drug Therapy in Chronic Childhood Iridocyclitis

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• The adjunctive use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of chronic iridocyclitis was evaluated in 14 patients, eight with juvenile rheumatoid arthritis and six with idiopathic iridocyclitis. In all patients, the activity of the iridocyclitis improved with the addition of NSAIDs to their treatment regimens, permitting reduction in the dose of corticosteroid drugs. These data suggest that NSAID therapy may have an adjunctive role in the treatment of chronic iridocyclitis in childhood.

(*AJDC* 1988;142:1289-1292)

Chronic iridocyclitis occurs in approximately 10% of patients with juvenile rheumatoid arthritis (JRA) and occasionally as idiopathic disease in the general pediatric population.[1-4] The incidence of chronic iridocyclitis is highest in patients with the pauciarticular subtype of JRA, which ranges from 19% to 34%.[1-3,5] The onset of chronic iridocyclitis in JRA is frequently insidious. Affected patients tend to be young and female. The development of chronic iridocyclitis in patients with JRA has also been associated with the presence of antinuclear antibodies (ANAs).[6,7]

For editorial comment see p 1281.

Therapy for iridocyclitis is aimed at suppressing inflammatory activity to preserve vision. Severe vision impairment (visual acuity of 20/200 or less) even with therapy has been described in up to 50% of patients with chronic iridocyclitis.[8-10] Early detection and corticosteroid therapy have been the mainstays in controlling this disease. However, chronic corticosteroid usage is, itself, associated with significant eye morbidity.

Fluctuations in disease activity of chronic iridocyclitis and arthritis in patients with JRA may not coincide. Since the nonsteroidal anti-inflammatory drug (NSAID) dosage that patients with JRA are receiving for treatment of arthritis may be decreased during periods of improvement in the arthritis, the effect of alterations of these medications on iridocyclitis may be important.

In this retrospective study, we reviewed our experience with the adjunctive effect of NSAID therapy on chronic iridocyclitis in eight patients with JRA and in six with idiopathic iridocyclitis (IIC).

METHODS

We reviewed the charts and management of all 23 patients with iridocyclitis in the pediatric arthritis clinic. The inclusion criteria for the study of pediatric patients with chronic iridocyclitis were as follows: patients who had at least one comprehensive evaluation in the pediatric arthritis clinic, had been followed up consistently by one of us (W.A.G.) for at least six months before and after starting NSAID therapy, and had received at least one trial of a daily oral NSAID. The patient records were evaluated for eye disease duration, level of eye disease activity, NSAID therapy, corticosteroid therapy, and laboratory tests, including those for ANAs and HLA-B27. The JRA subtype and joint-disease activity were recorded for patients with arthritis.

All patients had had careful systematic slit-lamp examinations at one- to 12-week intervals, depending on the disease activity. The intensity of inflammation in the anterior chamber had been graded on a standard 0 to +4 scale by one of us (W.A.G.). The number of inflammatory cells in the anterior chamber per slit-lamp beam (an area 1 mm wide and 3 mm high) was quantified per a standard grading scale as follows: 0 for less than four cells, +1 for five to ten cells, +2 for 11 to 20 cells, +3 for 21 to 50 cells, and +4 for greater than 50 cells.[11]

The corticosteroid dosage was quantified by identifying whether patients were receiving no corticosteroid therapy, topical corticosteroid therapy, alternate-day oral prednisone therapy, or daily oral prednisone therapy.

Statistical analysis was performed using a paired *t* test comparing the data at the onset of NSAID therapy with the data after six months of continual NSAID therapy. Values of $P<.05$ were considered significant.

PATIENTS

Of 23 patients with chronic iridocyclitis in our clinic, we identified 14 patients meeting these criteria, including eight patients with JRA and six with IIC. We excluded nine of 23 patients, as three had not received NSAIDs and six patients had insufficient ophthalmologic follow-up. The six patients with IIC had no identifiable connective-tissue disease on a thorough screening evaluation. Of the eight patients with JRA, six had pauciarticular-onset disease and two had polyarticular disease. At the time that daily long-term NSAID therapy was begun, the mean age of the patients with pauciarticular JRA was 15.5 years (range, 7 to 26 years); of the patients with polyarticular JRA, 10.5 years (range, 5 to 16 years); and of the patients with IIC, 17.2 years (range, 15 to 21 years). The mean duration of chronic iridocyclitis before starting daily long-term NSAID therapy in the patients with JRA was 3.4 years (range, one to five years), and in the patients with IIC, mean duration was 4.3 years (range, one to seven years). Twelve patients had been followed up by us longer than one year before and after starting

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Accepted for publication July 30, 1988.

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Presented in part at the 43rd Annual Meeting of the American Academy of Allergy and Immunology, Washington, DC, Feb 24, 1987.

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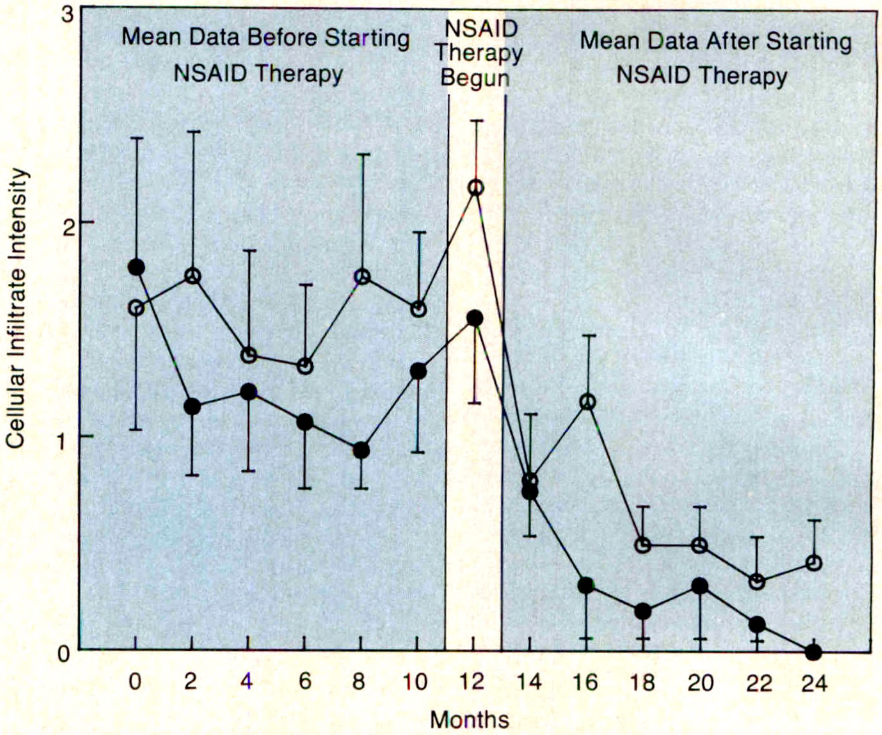
Table 1.—Selected Features of Patients With Iridocyclitis*

		No. of Patients			
Patient Group	**Mean Age (Range), y†**	**Sex, F-M**	**ANA Test, +/−‡**	**HLA-B27 +/−**	**Effective NSAID Therapy, Naproxen (Indomethacin)**
Pauciarticular JRA (n=6)	15.5 (7-26)	4:2	4/2	0/5 (1 NA)	5 (1)
Polyarticular JRA (n=2)	10.5 (5-16)	1:1	2/0	1/1	1 (1)
Idiopathic iridocyclitis (n=6)	17.2 (15-21)	2:4	1/3 (2 NA)	0/4 (2 NA)	3 (3)

*ANA indicates antinuclear antibody; plus sign, positive test results; minus sign, negative test results; NSAID, nonsteroidal anti-inflammatory drug; JRA juvenile rheumatoid arthritis; and NA, not available.

†Age when NSAID therapy for iritis was begun.

‡Serum titer greater than or equal to 1:20.



Iridocyclitis response to nonsteroidal anti-inflammatory drug (NSAID) therapy. Mean and SEM number of inflammatory cells in anterior chamber of eye in eight patients with juvenile rheumatoid arthritis (solid circles) and six patients with idiopathic iridocyclitis (open circles) are represented 12 months before (with exception of one patient in each group who is included six months before) and 12 months after initiation of NSAID therapy.

NSAID therapy. One patient with JRA and one with IIC had been followed up six months before and 12 months after starting NSAID therapy.

One of seven patients with JRA tested positive for HLA-B27 antigen. This patient with polyarticular JRA had no clinical or roentgenographic evidence of spondylitis, sacroiliac disease, or hip disease. None of four patients with IIC tested positive for HLA-B27 antigen. Six of eight patients with JRA tested positive for ANAs (≥1:20). One of four patients with IIC tested positive for ANAs. Further patient characteristics are listed in Table 1.

At the time long-term NSAID therapy was begun, some of these patients had previously received either short-term (less than four-week) courses of NSAID therapy or salicylate therapy for their mild arthritis and corticosteroid therapy for their eye disease. In all patients, long-term therapy had been started with daily oral naproxen (dosage range, 10 to 15 mg/kg/d), tolmetin sodium (dosage range, 30 to 40 mg/kg/d), or indomethacin (dosage, 1 to 2 mg/kg/d) for either their arthritis or chronic iridocyclitis. The severity and chronicity of the iridocyclitis or arthritis influenced the particular choice of NSAID used. Indomethacin was only used in patients over 12 years of age. In five of 14 patients, the initial long-term NSAID therapy attempted was discontinued after a four-month trial due to lack of eye disease improvement, and therapy with a second NSAID was begun.

Topical corticosteroids were administered in all eight patients with JRA. Four of eight patients had also required courses of oral corticosteroids with daily or alternate-day administration to control the eye inflammation. No patients were receiving remittive agents or corticosteroids for treatment of their arthritis.

One patient with IIC had both anterior and posterior uveal tract inflammation. All of these six patients had required topical corticosteroid therapy. Three of the six patients had required oral corticosteroid therapy, one receiving a two-week daily course and two receiving long-term alternate-day therapy.

RESULTS

All 14 patients' conditions improved with the addition of the effective NSAID to their regimen. This improvement was evidenced by a reduction of inflammatory cells in the anterior chamber of the eye in the eight patients with JRA ($P<.01$) and in the six patients with IIC ($P<.01$). One patient with IIC involving both the anterior and posterior uveal tracts had clearing of mild anterior chamber inflammation as well as over 50% improvement of severe macular edema with NSAID therapy. The responses in the inflammatory cells in the anterior chamber before and after NSAID therapy for all patients are illustrated

Table 2.—Corticosteroid Regimens Before and After NSAID Therapy*

Corticosteroid Therapy	No. of Patients by Months												
	Before Starting NSAID Therapy						NSAID Therapy Begun	After Starting NSAID Therapy					
	0	2	4	6†	8	10	12	14	16	18	20	22	24
Daily oral	2	1	0	1	1	1	3	0	0	0	0	0	0
Alternate day	2	2	2	2	2	2	2	3	2	2	2	2	1
Topical only	8	7	8	9	10	10	8	10	9	4	4	4	5
None	0	2	2	2	1	1	1	1	3	8	8	8	8

*The number of patients receiving each type of corticosteroid regimen is depicted at two-month intervals before and after starting nonsteroidal anti-inflammatory drug (NSAID) therapy.

†Data are included for two patients beginning six months before starting NSAID therapy.

in the Figure (values are the mean ± SEM).

The improvement following NSAID therapy permitted significant reduction in the dosage of corticosteroids in the eight patients with JRA ($P<.01$) and in the six patients with IIC ($P<.005$). In 12 of 14 patients requiring corticosteroid therapy six months before beginning NSAID therapy, corticosteroid requirements could not be reduced significantly. Six months after starting NSAID therapy, eight of 14 patients had discontinued all corticosteroid therapy. Of six patients still requiring corticosteroid therapy after six months of NSAID therapy, none was receiving oral prednisone daily, two were receiving oral prednisone on alternate days, and four were receiving topical corticosteroid therapy. This improvement in the corticosteroid dosage is illustrated in Table 2.

The long period of patient ophthalmologic assessment (six to 12 months) before NSAID therapy permitted establishment of each patient's baseline disease activity for comparison with disease activity while receiving NSAID therapy. With long-term daily NSAID therapy, improvement in the eye inflammation began after two months of therapy, with a continued decrease in inflammation intensity over a period of two to six months.

COMMENT

The iridocyclitis of JRA often has an insidious onset with a chronic course and few symptoms, especially in younger children. Pauciarticular JRA is associated with chronic iridocyclitis and is the subtype of JRA in which the joint disease is often readily controlled. The prompt therapeutic response of the arthritis may make it more likely for the eye disease to go undetected. Since irreversible visual loss may occur even in previously asymptomatic patients, it becomes important in young patients with pauciarticular JRA to obtain slit-lamp eye examinations every three months. Less-frequent examinations are required in other subtypes of JRA and in older children with pauciarticular JRA, as they are more likely to verbalize mild eye symptoms. Exacerbations of the eye disease and exacerbations of the arthritis are often unrelated. During periods of improvement of the arthritis, the NSAID dosage may be reduced and any effect of the NSAID dosage change on the eye disease is important to assess.

Early detection of eye disease and active treatment with corticosteroids are important in the management of chronic iridocyclitis. Chylack[3] reported an improved outcome in 36 patients with chronic iridocyclitis and JRA who were treated actively with topical or systemic corticosteroids and in some cases with sub–Tenon's capsule injections of corticosteroids. In these 36 patients, only 20% had progression of eye disease during the study. Achieving control of the eye disease often requires long-term corticosteroid therapy, and the ocular side effects of this therapy may contribute to loss of vision. Topical corticosteroid therapy in the eye may also contribute to cataracts, scleral thinning, and glaucoma.

Due to the immunomodulatory and anti-inflammatory effects of NSAIDs, they have potential to be useful in the treatment of chronic eye inflammation and have been used in the treatment of the acute form of anterior uveitis with some success. March and Coniglione[12] described two patients with acute anterior uveitis, one with ankylosing spondylitis and one with JRA, who were treated successfully with oral ibuprofen. Dunne et al[13] reported a series of patients with acute anterior uveitis who were treated with either topical corticosteroids or topical tolmetin sodium and reported no significant difference between the treatment groups. Giordano[14] reported improvement in acute anterior uveitis in two patients with ankylosing spondylitis treated with a combination of hydroxychloroquine sulfate and ketoprofen, with one patient also receiving diclofenac sodium. No studies of the effects of NSAID therapy on chronic iridocyclitis have been reported to date, to our knowledge.

In our patients, the addition of an NSAID to therapy for chronic iridocyclitis afforded additional improvement in the eye disease over a six-month period, permitting reduction in the corticosteroid dosage. The gradual nature of improvement in the eye inflammation may explain the reason improvement following short courses of NSAID therapy was not detected. There may also be individual variation in the response to a particular NSAID, thus requiring the trial of a second NSAID in some patients. In this study there did not appear to be a difference in eye disease response to long-term daily NSAID therapy between patients with IIC and those with JRA, possibly due to the small patient numbers.

Prospective controlled studies are needed to confirm these findings and delineate relative efficacy of various NSAIDs in the treatment of chronic iridocyclitis.

Our data suggest that oral NSAID therapy may affect anterior chamber inflammation. Therefore, it is important to consider the effect on the eye disease when changing, discontinuing, or adjusting the dosage of a NSAID in a patient with JRA. At these points of therapeutic change, more frequent follow-up of the eye disease may be necessary. These preliminary data suggest that adjunctive oral NSAID therapy may be helpful in a patient with JRA with poorly controlled chronic iridocyclitis even if the patient is not requiring anti-inflammatory drug therapy for arthritis. Similarly, a change in the NSAID used may be beneficial if the eye disease is not adequately controlled via treatment with the initial NSAID. Adjunctive oral NSAID therapy may also be helpful in patients with chronic iridocyclitis, particularly those requiring long-term corticosteroid therapy or experiencing unacceptable side effects of corticosteroid therapy.

References

1. Calabro JJ, Parrino GR, Atchoo PD, et al: Chronic iridocyclitis in juvenile rheumatoid arthritis. *Arthritis Rheum* 1970;13:406-413.
2. Schaller J, Kupfer C, Wedgwood RJ: Iridocyclitis in juvenile rheumatoid arthritis. *Pediatrics* 1969;44:92-100.
3. Chylack LT Jr: The ocular manifestations of juvenile rheumatoid arthritis. *Arthritis Rheum* 1977;20(suppl):217-223.
4. Cassidy JT, Sullivan DB, Petty RE: Clinical patterns of chronic iridocyclitis in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1977;20(suppl):224-227.
5. Lindsley CB: Pauciarticular juvenile rheumatoid arthritis, in Miller JJ III (ed): *Juvenile Rheumatoid Arthritis.* Littleton, Mass, PSG Publishing, 1979, pp 135-147.
6. Schaller JC, Johnson GD, Holborow EJ, et al: The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis. *Arthritis Rheum* 1974;17:409-416.
7. Kornreich HK, Drexler E, Hanson V: Antinuclear factors in childhood rheumatic diseases. *J Pediatr* 1966;69:1039-1045.
8. Smiley WK: The eye in juvenile rheumatoid arthritis. *Eye* 1974;94:817-828.
9. Key SN, Kimura SJ: Iridocyclitis associated with juvenile rheumatoid arthritis. *Am J Ophthalmol* 1975;80:425-429.
10. Vesterdal E, Sury B: Iridocyclitis and band-shaped corneal opacity in juvenile rheumatoid arthritis. *Acta Ophthalmol* 1950;28:321-337.
11. Hogan MJ, Kimura SJ, Thygeson P: Signs and symptoms of uveitis: Anterior uveitis. *Am J Ophthalmol* 1959;47:155-170.
12. March WF, Coniglione TC: Ibuprofen in the treatment of uveitis. *Ann Ophthalmol* 1985;17:103-104.
13. Dunne JA, Jacobs N, Morrison A, et al: Efficacy in anterior uveitis of two known steroids and topical tolmetin. *Br J Ophthalmol* 1985;69:120-125.
14. Giordano M: Dauerprophylaxe der rezidivierenden 'Spondylitischen Iridocyclitis' durch Antimalarica und nichtsteroidale Antiphlogistica. *Z Rheumatol* 1982;41:105-106.

Book Review

Vaccines, by Stanley Plotkin and Edward Mortimer, 650 pp, $99, Philadelphia, WB Saunders Co, 1988.

Two of the world's experts in vaccine development and utilization have edited and compiled an impressive text that should serve as a standard for all of those who deal with any aspect of vaccine science and practice. This 32-chapter text covers all of the available vaccines and includes technologic, regulatory, public health, and legal considerations.

Each chapter is well written by one of the world authorities in that area and the editing appears even. The chapters are organized (for the vaccines) by a systematic approach, listing the major features of each. These subheadings both provide an internal index to each chapter and permit the text to be used as a reference source, for someone wishing to find a particular feature of a given vaccine, without consulting the index.

Noncontroversial vaccines are handled with detail, sufficient to provide both practitioner and scholar with useful information. Controversial vaccines, such as pertussis, influenza, and the various poliovaccines, are presented in a clear, informative fashion, permitting exploration of the issues involved. Obviously, the authors of these latter chapters have a point of view, but they present their "bias" in scientific, nonemotional prose. Particularly noteworthy are the separate chapters on oral poliovirus vaccine and inactivated polio vaccine. In each, the experts (Melnick for oral polio vaccine, and Salk and Drucker for inactivated polio vaccine) present their reasoning for their recommendations. One minor conceit is evident in that inactivated poliovirus vaccine, the standard designation, is now entitled "noninfectious poliovirus vaccine," as if to underscore the infectivity of oral poliovirus vaccine.

As with all texts that deal with vaccines, some of the material is inevitably going to be out of date as soon as the text is published. Our information about the acellular pertussis vaccines, the newer conjugated *Haemophilus influenzae* type b vaccines and some others, is constantly accumulating, and no text can hope to capture such dynamic changes. However, the reader of this text is at least armed with the background information that will provide a framework into which the new information can be integrated.

I have little quarrel with the text, prose or figures. I did not like the quality of the paper used in the text. As a result, the print and figures, particularly the photographs, are reproduced poorly, in my view. I recognize that the costs of publication have increased dramatically in recent years, but for a text of this value to have such poor physical quality is disturbing.

This text should be useful in instruction of students and resident physicians, as an introduction to the immunology and practical use of vaccines for the practitioner, and as a valuable reference source for investigators and scholars in the disciplines involved.

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IgM-Enriched Intravenous Immunoglobulin Therapy in Neonatal Sepsis

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Muzamil H. Zaidi, BSc, MBBS; Hasan Bahakim, MD, FAAP

• Despite the development of newer generation of antibiotics, mortality from neonatal sepsis remains high. In a prospective, randomized study, we investigated the use of IgM-enriched immunoglobulin therapy in neonatal sepsis. Two groups of 30 infants each (matched for gestational age, sex, weight, and other variables) were randomly allocated to receive either antibiotics alone (control group) or antibiotics plus 5 mL/kg/d for four days of IgM-enriched immunoglobulin intravenously (immunotherapy group). Mortality from sepsis in the control group was 20% (6/30), while in the immunotherapy group it was 3.3% (1/30). We conclude that IgM-enriched immunoglobulin therapy in conjunction with antibiotic therapy significantly reduces mortality from neonatal sepsis.

(*AJDC* 1988;142:1293-1296)

Bacterial infections during the first month of life remain a major cause of mortality and morbidity despite improved perinatal care and the development of new-generation broad-spectrum antimicrobial drugs.[1-5]

Although mortality rates for early bacterial infection have declined by nearly 60% since 1930[6] in the developed countries, rates of 45% are still being reported in developing countries.[4,5]

The high mortality and morbidity rates despite improved antibiotics and technological advancements in life-support therapy have led to the search for other modalities of treatment.

Theoretical arguments for the use of immunoglobulin therapy in the newborn are very strong.[7] Parenteral immunoglobulin therapy has been shown to reduce mortality and severity of neonatal sepsis.[1,8,9] We[10] have shown a reduction in the rate of infection and mortality from neonatal sepsis in preterm and low-birth-weight infants using prophylactic intravenous immunoglobulin therapy. Herein, we report the results of our study using IgM-enriched intravenous immunoglobin in the *treatment* of neonatal sepsis.

PATIENTS AND METHODS

After approval from the ethics committee of the College of Medicine Research Center, Riyadh, Saudi Arabia, our study was conducted over a period of six months in the Special Care Baby Unit of the Maternity and Children's Hospital, Riyadh.

Sepsis in the neonate is not always easy to define objectively; thus, for this study, sepsis was defined as the presence of one or more clinical features, such as lethargy, instability of temperature, glucose intolerance, increased gastric aspirate, hepatosplenomegaly, as well as any two of the following laboratory variables: immature-to-total neutrophil ratio greater than 0.2, total white blood cell count either less than 5.0 or greater than 30.0×10^9/L (uncorrected for age), platelet count less than 50.0×10^9/L and a positive blood or cerebrospinal fluid (CSF) culture. For the purpose of analysis, when the diagnosis was based entirely on clinical and biochemical grounds, the cases were classified as "suspected sepsis," and the cases where the blood and/or CSF culture results were positive were classified as "proved sepsis." Infants with positive superficial skin swabs only were not included in this group.

Only infants with their first episode of sepsis were enrolled in the study. Whenever sepsis was suspected for the first time in a preterm infant (gestational age, 28 to 37 weeks), a sealed envelope was drawn, and the infant was allocated to receive either supportive and antibiotic therapy (control group) or supportive and antibiotic therapy plus 5 mL/kg/d of IgM-enriched intravenous immunoglobulin (Pentaglobin, Biotest Pharma, Frankfurt, West Germany), consisting of protein (250 mg), IgM (30 mg), IgA (30 mg), and IgG (190 mg) (immunotherapy group). Immunoglobulin therapy was administered over two hours per day for four days. The control group received 5 mL/d of 10% dextrose as placebo. The two solutions (IgM-enriched immunoglobulin and 10% dextrose) were dispensed in similar, unmarked bottles. The physician treating the infants was not aware of the contents. Prior to instituting therapy, a septic screening was performed. Blood was drawn for immunoglobulin assay and culture and white blood cell, differential, band, and platelet counts. Superficial skin swab, urine, and CSF cultures were performed, and a chest roentgenogram was obtained. The initial antibiotics used in both groups were ampicillin sodium (100 mg/kg/24 h) and gentamicin sulfate (3 mg/kg/24 h) in infants weighing less than 1 kg and 5 mg/kg/24 h in infants weighing more than 1 kg at birth (administered intravenously) until the culture results were available. Antibiotics were changed according to susceptibility-test results. These doses are currently used in our unit and are based on serum therapeutic levels. For the purpose of this study, the antibiotic therapy was continued for ten days, irrespective of the culture result.

Blood was also drawn from both groups of patients on the day of diagnosis (day 1) and on days 4, 7, and 10 for immunoglobulin assay. Immunoglobulins were assayed by rate nephlometry using the Beckman (Brea, Calif) automated immunochemistry system. Standard manufacturer's controls were used. Infants of mothers with history of allergic disorders or intrauterine infection were not included in the study, nor were infants with obvious congenital malformations.

For each infant enrolled in the study, the following information was recorded: maternal obstetric history, evidence of maternal infection, history of prolonged rupture of

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Accepted for publication Aug 23, 1988.

From the Department of Paediatrics, Division of Neonatology (Professor Haque) and College of Medicine Research Centre (Dr Bahakim), College of Medicine; and the Maternity and Children's Hospital (Dr Zaidi), Riyadh, Saudi Arabia.

Reprint requests to the Department of Paediatrics, College of Medicine, PO Box 2925, Riyadh 11461, Saudi Arabia (Professor Haque).

Table 1.—Basic Data for the Two Groups

	Range (Mean)					
Group	Gestational Age, wk	Birth Weight, kg	M/F Ratio	Mean Apgar Score at 5 min	No. of Infants Small for Gestational Age	No. of Infants With PROM*
Control (n = 30)	28-37 (35)†	0.9-1.7 (1.48)	20/10	7	2	4
Immunotherapy (n = 30)	28-37 (33.4)†	0.85-1.6 (1.32)	24/6	7	1	5

*PROM indicates prolonged rupture of membranes (longer than 24 hours).
†P = not significant.

membranes (longer than 24 hours), any antibiotic therapy, mode of delivery, Apgar score, gestational age, sex, birth weight, signs of sepsis, course of hospital stay, and outcome. For calculating the difference in the outcome, Student's *t* test was applied.

RESULTS

There were 30 infants in each group who were comparable with regard to gestational age, sex, birth weight, and Apgar score at five minutes (Table 1).

In the immunotherapy group, there were 21 cases of proved sepsis and nine cases of suspected sepsis, while in the control group there were 23 cases of proved sepsis and seven cases of suspected sepsis.

Table 2.—Number of Infections, Causative Organisms, and Outcomes in the Two Groups

Group	No. of Infections	Organisms (No. of Cases)	Mortality, No. (%)
Control			
Proved sepsis	23	*Escherichia coli* (10) *Klebsiella pneumoniae* (5) *Salmonella* species (4) *Staphylococcus epidermidis* (3) *Serratia* species (1)	4 (20)*
Suspected sepsis	7	. . .	2
Immunotherapy			
Proved sepsis	21	*E coli* (8) *K pneumoniae* (6) *S epidermidis* (2) *Salmonella* species (3) *Serratia* species (1) *Pseudomonas aeruginosa* (1)	1 (3.3)*
Suspected sepsis	9	. . .	0

*$P < .001$.

The number of infections, causative organisms, and the outcome in each group are shown in Table 2. Applying Student's *t* test, there was a significant difference in the outcome of the two groups: six infants (20%) died in the control group, while only one infant (3.3%) died in the immunotherapy group ($P < .001$).

Escherichia coli was the most frequent organism isolated, being responsible for 43.4% of infections in the control group and 38% of infections in the immunotherapy group. There were two cases of *E coli* meningitis in each group. Other significant organisms were *Klebsiella* (21.7% in the control group and 28.5% in the immunotherapy group); *Salmonella* (17.3% in the control group and 14.2% in the immunotherapy group), and *Staphylococcus epidermidis* (13% in the control group and 9.5% in the immunotherapy group).

There were no unusual antibacterial sensitivities noted from the cultures obtained either from the control or the immunotherapy group. One infant in the treatment group had a urinary tract infection, compared with no infants in the control group. Pneumonia was diagnosed in four infants in the immunotherapy group and in five infants in the control group (P = not significant). Mean age at diagnosis was 54.6 hours (range, 18 to 96 hours); there was no significant difference in age between the two groups, nor was there any significant difference between the two groups in the mode of delivery and the Apgar score.

Serum immunoglobulin results are shown in Figs 1, 2, and 3. There was a significant ($P < .001$) difference in the mean values of serum IgM on days 7 and 10. The serum IgG levels were high in both groups, with considerable overlap. Serum IgA levels achieved a significant difference ($P < .01$) on day 10. The platelet and white blood cell counts returned to normal earlier in the immunotherapy group than in the control group, but the difference was not statistically significant.

COMMENT

Scores of new generations of antibiotics are brought into the market every year, improving the treatment of neonatal sepsis and reducing antibiotic-related toxicity.[8,11] Infection still remains a major cause of mortality and morbidity in newborns.[1-5,11,12]

Over the past decade, interest in immunoglobulin as an immunotherapeutic agent has evolved through the availability of human immunoglobulin preparations suitable for intravenous administration[13] and through advances in our understanding of the role of type-specific antibody in the protection of the newborn infant against invading organisms, particularly against invasive group B streptococci.[14-16]

Wasserman[17] stated that "The theoretical arguments supporting the use of supplementary gamma globulin in certain newborns is very strong . . . there is solid evidence that infants who develop sepsis lack specific protective antibodies against the infecting organisms, and the specific immune system (antibody production and T cells) are too slow to have an impact on bacterial disease in the newborn."

Steen[18] and Amer et al,[19] using the first generation of intramuscular immunoglobulin preparations (gamma globulin) to prevent neonatal sepsis, found them not particularly useful. It

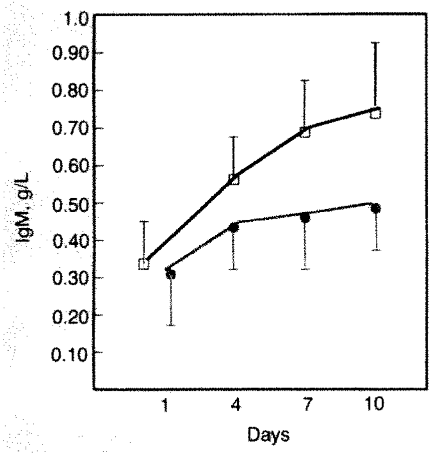

Fig 1.—Serum IgM concentrations in treated group (squares) and control group (circles). Using Student's *t* test, difference in mean values on days 7 and 10 was $P<.001$. Vertical bars indicate SD. Day 1 denotes day of diagnosis.

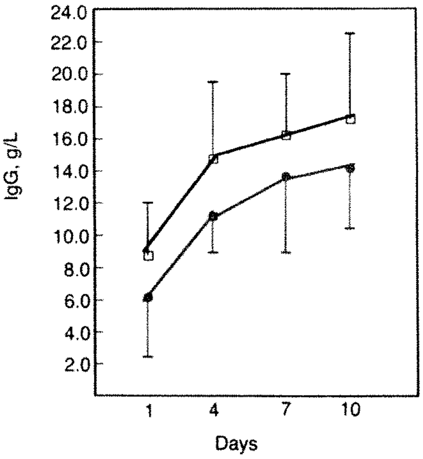

Fig 2.—Serum IgG concentrations in treated group (squares) and control group (circles). Using Student's *t* test, difference in mean values was not significant. Vertical bars indicate SD. Day 1 denotes day of diagnosis.

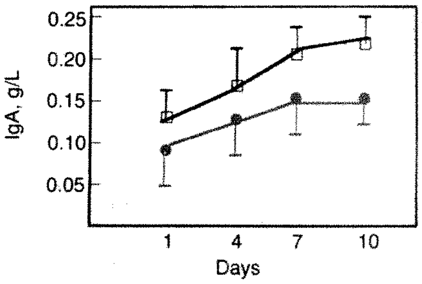

Fig 3.—Serum IgA concentrations. Using Student's *t* test, difference in mean values on day 10 was $P<.01$. Vertical bars indicate SD. Day 1 denotes day of diagnosis.

was not until 1981 that Sidiropoulos et al[1] showed the beneficial effects of intravenous immunoglobulin therapy in neonatal sepsis. Fisher et al,[20] in 1984, reported the efficacy and pharmacokinetics of intravenous immunoglobulin therapy in infants with group B streptococcal sepsis. To our knowledge, we[10] were the first to show that prophylactic intravenous immunoglobulin therapy reduced the incidence and mortality from neonatal sepsis in preterm and low-birth-weight infants.

In our previous study,[10] we used an immunoglobulin preparation, intraglobin (Biotest Pharma, Frankfurt, West Germany), that contained 4.9 g of IgG, 0.03 g of IgA, and 0.02 of IgM per 100 mL. Eight and 12 days after infusion of this preparation, not only had the serum IgG increased ninefold but serum IgM had also increased sixfold. A similar increase in IgG level had been shown by Sidiropoulos et al[1] after infusion of intravenous immunoglobulin therapy, but the rise in serum IgM level remained inexplicable. We think this may be the result of increased antigenic recognition induced by intravenous immunoglobulin therapy or due to the immunomodulatory effect of the gammaglobulin preparation infused.

We wondered whether this rise in serum IgM level overcame the physiological transitory lack of IgM in these neonates[21] and was responsible for the favorable outcome in our study. We therefore decided to study the effect of IgM-enriched immunoglobulin in the treatment of sepsis. There are many theoretical reasons why boosting the serum IgM level in the newborn would help the infant in combating sepsis: (1) IgM is the first specific antibody in immune response—its titers rise before those of IgG[21]; (2) IgM requires a less-extensive cascade of cooperating cells and factors than IgG, leading to a more rapid and specific antibody response,[22] particularly important in preterm newborn infants who may lack maternal IgG; (3) IgM has the ability to fix complement, which can enhance opsonization, thus playing an important role in the elimination of bacteria; and (4) IgM alters the cell-wall characteristics of the antigen, initiating its lysis or intracellular lysis after phagocytosis.[23]

We used Pentaglobulin (Biotest Pharma) because it contained 12% IgM of the total protein (5 g/100 mL). Its ingredients are listed in the tabulation below (manufacturer's data):

Ingredient per 100 mL	Amount
Protein	5.0 g
Human immunoglobulin	95%
IgM	0.6 g
IgA	0.6 g
IgG	3.8 g
Glucose	2.5 g
Sodium chloride	0.45 g
Water for injection	add water to make volume to 100 mL

Pentaglobin also has high antibody titers against the most frequent organisms seen in the Children's Hospital nursery (see tabulation below):

Organism	Titer
E coli	640-1280
S epidermidis	64-128
Streptococcus faecalis	160
Staphylococcus aureus	160-320
Klebsiella pneumoniae	1280-2560
Pseudomonas aeruginosa	640-1280
Streptococcus viridans	160
Streptococcus pyogenes	160-320
Proteus vulgaris	64

This preparation retains the property to neutralize endotoxins by having a high concentration of anti–lipid A antibodies and antibodies against other lipopolysaccharide determinants. According to the manufacturers, it is prepared by Cohn fractionation and by treatment with propiolactone of radioimmunoassay hepatitis B surface antigen–negative pooled plasma from at least 1000 healthy donors and meets the current standard safety tests set by the European Pharmacopia. Moreover, earlier studies with Pentaglobulin in adult patients suffering from infection in surgical and intensive care units had shown its efficacy and safety.[24]

Most of the literature about intravenous immunoglobulin therapy relates to group B streptococci,[16,20,23,25,26] except for the studies by Sidiropoulos et al,[1] us,[10] and Chirico et al.[27] At the time of this writing, we are not aware of any study in the English literature on the use of IgM-enriched intravenous immunoglobulin in either the prevention or treatment of neonatal sepsis. With the concomitant use of IgM-enriched intravenous immunoglobulin therapy and broad-spectrum antibiotic therapy, we were able to reduce the mortality of neonatal sepsis from 20% to 3.3% ($P<.001$). There were no major side effects of the therapy (two infants showed some hemolysis when they were given the preparation rapidly). The degree of hemolysis was mild. The hemoglobin level fell by 14 and 18 g/L while the reticulocyte count rose to 7% and 11%, respectively. Coombs' tests were negative, and the two infants did not require any therapy for this. Although we are not certain as to the cause of hemolysis, it is unlikely to be due to anti–A and anti–B hemolysins, as their level in the preparation was not recordable. Intravenous immunoglobulin therapy is expensive, but the cost benefits in terms of human life are incalculable, particularly in nurseries where the infection rate is high.

Our data strongly suggest that IgM-enriched intravenous immunoglobulin preparations, like IgG preparations, offer a major advance in the treatment of neonatal sepsis. However, it remains to be determined whether IgM-enriched immunoglobulin preparations are superior to the more standard intravenous immunoglobulin preparations. To answer this question, we are currently conducting a double blind trial with IgM-enriched and standard gammaglobulin preparations.

References

1. Sidiropoulos D, Bhome U, von Muralt G, et al: Immunoglobulin substitution in the treatment of neonatal sepsis. *Schweiz Med Wochenschr* 1981;111:1649-1655.
2. Oto A: Major bacterial infections in a referral neonatal intensive care unit. *J Infect* 1982;5:117-126.
3. Omene JA: Neonatal septicemia in Benin City, Nigeria. *Trop Geogr Med* 1979;31:35-39.
4. Ohlsson A, Serenius F: Neonatal septicemia in Riyadh, Saudi Arabia. *Acta Paediatr Scand* 1981;70:825-829.
5. ElRifai MR: A study of 214 neonates with infection in Maternity and Children's Hospital, Riyadh, Saudi Arabia. *Ann Trop Paediatr* 1982;3:119-122.
6. Freedman RM, Ingram DL, Gross I, et al: A half century of neonatal sepsis at Yale. *AJDC* 1981;135:140-144.
7. Yoder MC, Polin RA: Immunotherapy of neonatal septicemia. *Pediatr Clin North Am* 1986;33:481-501.
8. Lindquist L, Lundberg P, Massing R: Pepsin treated human gamma-globulin in bacterial infection. *Vox Sang* 1981;40:329-338.
9. Conway SP, Gillies DRN, Docherty A, et al: The effect of weekly intramuscular gamma-globulin on infection-related morbidity and mortality in the premature baby. *Paediatr Rev Commun* 1987;1:277-289.
10. Haque KN, Zaidi MH, Haque SK, et al: Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants. *Pediatr Infect Dis J* 1986;5:622-625.
11. Klein JO, Dashefsky B, Norton CR: Selection of antimicrobial agents for the treatment of neonatal sepsis. *Rev Infect Dis* 1983;5(suppl 1): S55-S64.
12. McCraken GH Jr: Bacterial and viral infections in the newborn, in Avery GB (ed): *Neonatology, Pathophysiology and Management of the Newborn*, ed 2. Philadelphia, JB Lippincott, 1983, p 723.
13. Alving BM, Finlayson JS: *Characteristics and Uses of Intravenous Preparations.* US Dept of Health and Human Services publication 80-9005. Washington, DC, US Government Printing Office, 1980.
14. Baker CJ, Edwards MS, Kasper DL: Role of antibody to native type 111 polysaccharide of group B streptococcus in infant infection. *Pediatrics* 1981;68:544-549.
15. Hemming VG, Hall RT, Rhodes PG, et al: Assessment of group B streptococcal opsonins in human and rabbit serum by neutrophil chemiluminescence. *J Clin Invest* 1976;58:1379-1387.
16. Vogel LC, Kretschmer RR, Padnos DM, et al: Protective value of gammaglobulin preparations against group B streptococcal infections in chick embryos and mice. *Pediatr Res* 1980;14:788-792.
17. Wasserman RL: Intravenous gammaglobulin prophylaxsis for newborn infants. *Pediatr Infect Dis* 1986;5:620-621.
18. Steen JA: Gammaglobulin in preventing infections in premature infants. *Arch Pediatr* 1960;77:291-294.
19. Amer J, Olt E, Ibbolt FA, et al: The effect of monthly gammaglobulin administration on morbidity and mortality from infection in premature infants during first year of life. *Pediatrics* 1963;32:4-9.
20. Fisher GW, Weisman LB, Hemming VG, et al: Intravenous immunoglobulin in neonatal group B streptococcal disease. *Am J Med S* 1984;76(suppl):117-123.
21. Van Furth R, Schuit HRE, Hijmans W: The immunological development of the human fetus. *J Exp Med* 1965;122:1173-1188.
22. Urquhart GED: Serum IgM and IgA responses in influenza A infections. *J Clin Pathol* 1974;27:198-201.
23. Stubner G: Indirect evidence of cell wall alterations in *Pseudomonas aeruginosa* by immunoglobulin preparations. *Infection* 1984;12: 223-224.
24. Just HM, Metzger M, Vogel W, et al: Therapeutic effects of immunoglobulins in ICU patients with severe infection, abstract S1-05. *Abstracts of the 18th Congress of the International Society of Blood Transfusion, Munich,* July 22-27. Basel, Switzerland, Karger-Verlag, 1984.
25. Christensen KK, Christensen P, Bucher HU, et al: Intravenous administration of human IgG to newborn infants: Changes in serum antibody levels to group B streptococci. *Eur J Pediatr* 1984;143:123-127.
26. Christensen KK, Christensen P, Duc G, et al: Human IgG antibodies to carbohydrate and protein antigens in mouse protection tests with group B streptococci. *Pediatr Res* 1984;18:478-482.
27. Chirico G, Rondini G, Plebani A, et al: Intravenous gammaglobulin therapy for prophylaxis of infection in high-risk neonates. *J Pediatr* 1987;110:437-442.

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Review

Peroxisomal Disorders

Biochemical and Clinical Diagnostic Considerations

Inderjit Singh, PhD; Graeme H. Johnson, MB, ChB; Frank R. Brown III, PhD, MD

• The peroxisomal disorders are a group of inherited metabolic diseases with serious clinical sequelae. The number of recognized peroxisomal disorders has increased substantially since 1973, when an absence of peroxisomes was observed in patients with the cerebro-hepato-renal (Zellweger's) syndrome. More subtle peroxisomal dysfunction is now recognized, including that deriving from single peroxisomal enzymes. Peroxisomal disorders are relatively rare. However, these disorders assume importance because of our growing ability to relate clinical sequelae to specific enzymatic and biochemical deficits, because some of these disorders can now be identified prenatally and their recurrence can be prevented, and because therapies are rapidly evolving. We reviewed these disorders in light of increasing understanding of the biochemistry of the peroxisome.

(*AJDC* 1988;142:1297-1301)

Biochemical research is disclosing an increasing number of inherited disturbances of metabolic function of subcellular organelles such as mitochondria, lysosomes, and peroxisomes. In a number of these metabolic disorders there are sequelae that are important to the clinician. The peroxisomal disorders are a newly recognized group of such inherited metabolic disorders in which serious clinical sequelae result from defects in either single enzymes found in the peroxisome or impairment of multiple peroxisomal enzymatic functions. Since the observation in 1973[1] that peroxisomes were lacking in patients with Zellweger's syndrome, or the cerebro-hepato-renal syndrome (CHRS), there has been rapid progress in delineation of specific biochemical defects in several peroxisome-based disorders. Aspects of this progress have been reviewed previously.[2,3] The present article addresses the challenge of integrating rapidly expanding biochemical information on peroxisomal function into useful biochemical and clinical diagnostic categories.

BIOCHEMICAL BACKGROUND

Peroxisomes were first described in 1954 by Rhodin[4] as organelles in rat kidneys. Rhodin reported them to be approximately 0.5 μm in diameter, surrounded by a single membrane, and filled with a fine granular matrix. Rhodin referred to these structures as "microbodies." DeDuve and coworkers[5] characterized these organelles as being biochemically distinct and, based in part on their understood biochemical properties, named them peroxisomes. Since then peroxisomes have been found universally in eukaryotic cells, although their functions in the mammalian metabolism remained unclear until recently.

Lazarow and DeDuve[6] have emphasized the role of peroxisomes in fatty acid β-oxidation. Peroxisomes contain a specific β-oxidation enzyme system that is distinct from that system found in mitochondria.[7] More recently, Singh et al[8] demonstrated that the major part of β-oxidation of very-long-chain fatty acids (VLCFA) ($>C_{22}$) takes place in peroxisomes. In addition to these specific oxidases, peroxisomes also contain oxidases related to D-amino and L-amino acids, urate, alcohols, polyamines, and α-hydroxy acids.[9] Peroxisomes can be identified by catalase that is active on the hydrogen peroxide produced in these oxidative processes. Peroxisomal enzyme functions also relate to the biosynthesis of bile acids[10] and ether-phospholipids such as plasmalogens and alkylglycerophospholipids.[11] The latter function involves the enzyme dihydroxyacetonephosphate-acyltransferase (DHAP-AT) and the ether-linked phospholipids are important in membrane and myelin structure. Catabolic pathways using peroxisomal enzymes include those of phytanic acid,[12] dicarboxylic acids,[13] and pipecolic acid (an intermediate in lysine metabolism).[14] The enzyme for transamination of glyoxylate to glycine is also predominantly peroxisomal.[15]

CLASSIFICATION OF PEROXISOMAL DISORDERS

Table 1 shows the known biochemical abnormalities in the peroxisomal disorders identified to date, which may be grouped as follows:

1. Those that represent more diffuse peroxisomal dysfunction due to (a) a reduction in the number of peroxisomes, often reflecting a defect in peroxisomal assembly; and (b) normal numbers of peroxisomes, but reduced activities of multiple peroxisomal enzymes.
2. Those disorders that reflect specific single peroxisomal enzymatic defects.

Diffuse Enzyme Defects (Group 1)

Group 1a differs from group 1b in that peroxisomes can be identified in group 1b by catalase cytochemical staining. While peroxisomes are present in group 1a, they are not demonstrable by the catalase cytochemical stain because they lack catalase as well as other matrix proteins. Peroxi-

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Accepted for publication July 19, 1988.

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somes in group 1a are referred to as ghost peroxisomes.[16] Ghost peroxisomes can be identified immunocytochemically with antibodies against peroxisomal membranes. Since peroxisomes in group 1a lack matrix proteins and some of the matrix proteins are present in cytosol (eg, catalase), it has been suggested that a defect exists in peroxisomal assembly in disorders identified as belonging in group 1a.

Diseases in which there appears to exist more diffuse dysfunction of the peroxisome, including a reduction in the number of peroxisomes and multiple peroxisomal enzymatic functions, include CHRS, the neonatal form of adrenoleukodystrophy (ALD), hyperpipecolic acidemia, the infantile form of Refsum's disease, and the rhizomelic form of chondrodysplasia punctata.

The observation that peroxisomes are absent from hepatic cells of patients with CHRS makes this the prototype (and perhaps the most devastating example) of disorders involving multiple peroxisomal functions. Affected children can usually be identified neonatally by marked hypotonia with associated characteristic dysmorphic features (eg, flat high forehead with open sutures, flat occiput, and reduced orbital ridges).[17] Cataracts, retinitis pigmentosa, jaundice, and hepatomegaly may also occur. Beyond the neonatal period, the child with CHRS will manifest obvious psychomotor retardation with or without seizure disorder. Micronodular cirrhosis, renal cysts, and stippled calcification of the knees and hips are less constant clinical features of the evolving disorder. Abnormal neuronal migration patterns are seen on microscopic examination of brain tissue.

Neonatal ALD presents with facial dysmorphisms and hypotonia similar to those features observed in CHRS.[18-20] It is, however, a separate disorder with an absence of renal cysts, cataracts, or bony involvement.[21] Adrenal dysfunction, a major feature of neonatal ALD, does not occur in CHRS.

Hepatomegaly and progressive hypotonia and psychomotor retardation have also been reported in cases of hyperpipecolic acidemia. Biochemical and microscopic changes of the brain are similar to those found in CHRS. However, patients do not have the characteristic physiognomy and have retinal pigmentary changes that are not prominent in CHRS.

Abnormalities in phytanic acid metabolism have been recognized to be associated with facial dysmorphisms, hypotonia, psychomotor retardation, liver disturbances, and retinitis pigmentosa. Cases reported recently have shown considerable phenotypic variation.[22] Infantile Refsum's disease appears to fall within the rubric of peroxisomal disorders.[23]

Children with the rhizomelic form of chondrodysplasia punctata have characteristic shortening of proximal limb segments. They also have a low nasal bridge and flat profile similar to children with CHRS and neonatal ALD.[24] Cataracts and liver enlargement are present and roentgenograms show calcific stippling of the epiphyses. Development is retarded and the infants fail to thrive. Recent microscopic studies have shown unusual peroxisomal structure and there are deficiencies in the enzymes related to plasmalogen metabolism.[25] These findings suggest links to Conradi-Hunerman chondrodysplasia, which has similar features of delayed limb growth development and epiphyseal dysplasia.[26]

The prevalence of retinal pigmentary changes in peroxisomal disorders has led to a search for metabolic causes in disorders exhibiting such changes. This approach has been applied in Leber's amaurosis and it appears that, at least in some cases, such patients may have peroxisomal disorders that will require further delineation.[27]

Specific Enzyme Defects (Group 2)

Diseases in which there appears to exist a specific peroxisomal enzymatic dysfunction include the following: X-linked childhood ALD and its adult variant, adrenomyeloneuropathy; the adult form of Refsum's disease; acatalasemia; hyperoxaluria type 1; and pseudo-Zellweger's syndrome (peroxisomal thiolase deficiency).

In X-linked childhood ALD, the most commonplace example of a specific peroxisomal enzyme defect, the clinical presentation presumably stems from a defect in the oxidation of the VLCFA, causing their toxic accumulation.[8,28-32] The finding of normal oxidation of VLCFA acyl–coenzyme A (CoA) as compared with free VLCFA suggested a defect in the activation of VLCFA to acyl-CoA derivatives.[33-35] Deficient activity of VLCFA acyl-CoA ligase and normal oxidation of VLCFA acyl-CoA in isolated peroxisomes from cultured skin fibroblasts demonstrated the lack of VLCFA acyl-CoA ligase activity in X-linked childhood ALD.[36]

The usual age at onset of childhood ALD is 4 to 8 years, with an initial deterioration in school achievement, behavior, and/or memory. This may be followed, in variable order, by gait, speech, and swallowing difficulties, and loss of vision and/or hearing. This pattern progresses in most cases to decerebrate rigidity and death within two to three years. Adrenal hypofunction may be part of the clinical picture with "bronzing" of the skin.[37] There also occurs a later onset form of deficient catabolism of VLCFA known as adult adrenomyeloneuropathy.[38,39] In this more slowly progressive disorder there is more involvement of the spinal cord, peripheral nerves, and adrenal glands, with evolution of spastic paraparesis, progressive polyneuropathy, and addisonian symptoms.

Adult Refsum's disease results from the toxic accumulation of the methylated branched-chain fatty acid phytanic acid, producing a peripheral neuropathy, cerebellar ataxia, and retinitis pigmentosa. This autosomal recessive condition is rarer than ALD.[40]

Other rare disorders in this group are acatalasemia and hyperoxaluria type I. Acatalasemia shows some genetic variations, but typically cases present with gangrenous oral ulceration. Tissues lack the ability to decompose hydrogen peroxide produced in oxidative processes during infection.[41] In the autosomal recessive disorder hyperoxaluria type 1, nephrolithiasis, and renal deterioration secondary to recurrent calcium oxalate deposition occur. This is the result of excessive oxalate production secondary to failure of transamination of glyoxylate in the peroxisomes.[15]

Table 1.—Biochemical Classification of Peroxisomal Disorders*

Disorder	Basis for Biochemical Diagnosis	Specific Enzyme Deficiency in Peroxisomes
Group 1a (defects in peroxisomal assembly)		
Cerebro-hepato-renal syndrome (Zellweger's syndrome)	VLCFA ↑; PA ↑; PPA ↑; PL ↓	...
Neonatal adrenoleukodystrophy	VLCFA ↑; PA ↑; PPA ↑; PL ↓	...
Infantile Refsum's disease	VLCFA ↑; PA ↑; PPA ↑; PL ↓	...
Hyperpipecolic acidemia	VLCFA ↑; PPA ↑; PL ↓	...
Group 1b (multiple enzyme deficiency): rhizomelic chondrodysplasia punctata	PA ↑; PL ↓	...
Group 2 (specific enzyme deficiency)		
Childhood adrenoleukodystrophy (X-linked)	VLCFA ↑	VLC-CoA ligase
Adrenomyeloneuropathy (X-linked)	VLCFA ↑	VLC-CoA ligase
Adult Refsum's disease	PA ↑	PA-oxidase
Hyperoxaluria	OX ↑	A-G–aminotransferase
Acatalasemia	...	Catalase
Peroxisomal thiolase deficiency (pseudo-Zellweger's syndrome)	VLCFA ↑	3-keto acyl-CoA thiolase

*VLCFA indicates very-long-chain fatty acid; PA, phytanic acid; PPA, pipecolic Acid; PL, plasmalogens; OX, oxalate; A-G–aminotransferase, alanine-glyoxylate aminotransferase; upward-pointing arrow, plasma levels above normal range; downward-pointing arrow, plasma levels below normal range; and CoA, coenzyme A.

A report by Goldfischer et al[42] has called attention to an infant with so-called pseudo-Zellweger's syndrome. This child presented with clinical findings of CHRS (Zellweger's syndrome), but had microscopically normal peroxisomes. Biochemically, there was deficiency of only a single peroxisomal enzyme, 3-keto acyl-CoA thiolase (Table 1).[43] Investigation of similar patients may provide some important insights into peroxisomal metabolism.

INCIDENCE

At present the incidence of peroxisomal disorders is not definitely known, as many cases may not be recognized. However, recent discovery of many new cases of X-linked ALD and CHRS (the two most prevalent conditions) indicates rates may be higher than was first appreciated. Zellweger estimated the incidence of CHRS to be approximately one case in 25 000 to 50 000 newborns.[21]

DIAGNOSIS

Peroxisomal disorders should now be considered as part of the differential diagnosis in any infant with hypotonia and delays in psychomotor development, and especially in those children who additionally evidence facial dysmorphisms (particularly a high and prominent forehead), hepatomegaly, presence of cataracts and/or retinitis, calcific stippling, short limbs, or combinations of any of these features (Table 2). The presence of these disorders should also be entertained in school-age children with progressive neurologic changes, and in adults with history of a slowly progressive motor disorder, with or without retinitis. The clinical presentation can suggest a biochemical test or group of tests (Table

Table 2.—Clinical Characteristics in Peroxisomal Disorders*

	Condition							
Characteristic	XALD	AMN	NALD	CHRS	HPA	IR	RCD	PZ
Signs as neonate								
High forehead			++	++			++	
Hypotonia			++	++	++	+		+
Hepatomegaly			+	++	++			+
Cataract			+	++			++	
Retinal pigmentation			+	+	++	+		
Rhizomelia							++	
Signs as infant								
Psychomotor delay			++	++	++	++	++	++
Failure to thrive			++	++	++	+	++	+
Seizures			++	++	++	+		+
Hearing deficit			+	+	+	++	+	
Signs as child								
Loss of motor skills	++							
Progressive dementia	++							
Skin bronzing	+							
Signs as adult								
Spastic paraparesis		++						
Skin bronzing		+						
Pathology findings								
Reduced corticotropin response	++	++	++	+				
Calcific stippling				+			++	
Renal cysts				+				+
Neuronal heterotopias			++	++	+	+		++

*XALD indicates X-linked adrenoleukodystrophy; AMN, adrenomyeloneuropathy; CHRS, cerebro-hepato-renal syndrome (Zellweger's syndrome); NALD, neonatal adrenoleukodystrophy; HPA, hyperpipecolic acidemia; IR, infantile Refsum's disease; RCD, rhizomelic chondrodysplasia punctata; PZ, pseudo-Zellweger's syndrome; two plus signs, substantial sign or finding; and one plus sign, less substantial sign or finding.

1) that will lead to identification of the particular disorder within the peroxisomal disorder grouping.

In childhood-onset dementia with signs suggestive of X-linked ALD and in adults with progressive neuropathy or adrenal hypofunction suggestive of adrenomyeloneuropathy, measurement of VLCFAs is used to confirm or deny these diagnoses. This can be done using 1 mL of blood in heparin sent to a center able to perform gas-liquid chromatographic assay for VLCFA levels.[44,45] A test using filter paper samples has now been developed.[46] The specific assay of VLCFA acyl-CoA ligase can identify patients with X-linked ALD for research purposes.[36] In neonates presenting with hypotonia and dysmorphic features, assays for VLCFA should be supplemented with tests of bile acid, phytanic acid, and plasmalogen levels. The rhizomelic child with stippled calcification should undergo plasmalogen, phytanic acid, and DHAP-AT assessment.

Measurement of levels of VLCFA and their oxidation activity in chorionic villus fibroblasts or cultured amniocytes permits prenatal detection of many of the peroxisomal disorders listed in Table 1.[47] When needed, DHAP-AT activity and plasmalogen levels can also be used.[48] Microscopy can demonstrate the presence or absence of peroxisomes. These data can assist in making informed choices during pregnancy in affected families. Early postnatal diagnosis of CHRS by the use of filter paper blood samples measuring fatty acids, bile acids, and plasmalogens[49] is a step toward the possibility of early detection of this condition.

TREATMENT

Reduction of abnormal levels of metabolites in symptomatic patients with peroxisomal disorders does not appear to alter their clinical status. Despite normalization of levels, patients' conditions usually continue to deteriorate. An exception occurs when phytanic acid intake is controlled in adults with Refsum's disease. Phytanic acid is not an essential endogenously produced metabolite. As it circulates in the blood, plasmapheresis can be used to reduce the body load of phytanic acid present and simultaneous restriction of dietary intake will also control its level.[50]

In X-linked ALD, dietary restriction of VLCFAs has lowered their plasma levels. This has also been achieved by transplantation of normal bone marrow cells.[51] Clofibrate induces peroxisomal proliferation and the biogenesis of β-oxidation enzymes, but does not appear to be clinically helpful. Addition of glycerol trioleate to the diet may be a more promising therapy because it reduces the synthesis of $C_{22\text{-}26}$ fatty acids.[52,53] Glycerol trioleate is a lipid containing unsaturated fatty acid (oleic acid, $C_{18:1}$), which competes with saturated C_{18} fatty acids for the specific fatty acid elongation system that forms fatty acid chains longer than C_{18}. Use of glycerol trioleate competitively reduces the saturated VLCFA level, which appears to cause the damage; since unsaturated VLCFA appears to be nonpathogenic it should have minimal side effects.

Where there is only one pathway disturbed (eg, in childhood ALD) such manipulations may help as they control the accumulation of the metabolite, thereby, it is hoped, reducing toxicity. However, in the generalized or multiple-enzyme peroxisomal disorders there are no specific therapies currently available. Further studies are being undertaken in the areas of identification of enzyme activities, enzyme biogenesis and processing, and methods of control within the peroxisomal organelle. These studies may produce new ways in which metabolic disturbance may be manipulated to minimize the sequelae for the patient.

References

1. Goldfischer S, Moore CL, Johnson AB, et al: Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. *Science* 1973;183:62-64.
2. Moser HW: Peroxisomal disorders. *J Pediatr* 1986;108:89-91.
3. Schutgens RB, Heymans HS, Wanders RJ, et al: Peroxisomal disorders: A newly recognized group of genetic diseases. *Eur J Pediatr* 1986;144:430-444.
4. Rhodin J: *Correlation of Ultrastructural Organization and Function in Normal and Experimentally Changed Proximal Convoluted Tubule Cells of the Mouse Kidney,* thesis. Stockholm, 1954.
5. DeDuve C, Beaufay H, Jaques P, et al: Intracellular localization of catalase and some oxidases in rat liver. *Biochim Biophys Acta* 1960;40:186-187.
6. Lazarow PB, DeDuve C: A fatty acyl-CoA oxidizing system in rat liver peroxisomes: Enhancement by clofibrate: A hypoplipidemic drug. *Proc Natl Acad Sci USA* 1976;73:2043-2046.
7. Hashimoto T: Individual peroxisomal β-oxidation enzymes. *Ann NY Acad Sci* 1982;386:5-12.
8. Singh I, Moser AE, Goldfischer S, et al: Lignoceric acid is oxidized in the peroxisome: Implications for the Zellweger cerebro-hepatorenal syndrome and adrenoleukodystrophy. *Proc Natl Acad Sci USA* 1984;81:4203-4207.
9. Tolbert NE: Metabolic pathways in peroxisomes and glyoxysomes. *Ann Rev Biochem* 1981;50:133-157.
10. Kase F, Bjorkhem I, Peterson JI: Formation of cholic acid from 3,7,12-trihydroxy-5-cholestanoic acid by rat liver peroxisomes. *J Lipid Res* 1983;24:1560-1567.
11. Hajra AK, Bishop JE: Glycerolipid biosynthesis in peroxisomes via the acyl dihydroxyacetone phosphate pathway. *Ann NY Acad Sci* 1982;386:170-182.
12. Poulos A, Sharp F, Whiting M: Infantile Refsum's disease (phytanic acid storage disease): A variant of Zellweger syndrome? *Clin Genet* 1984;26:579-586.
13. Mortensen PB, Gregerson N, Rasmusisen K: The oxidation of dicarboxylic acids in isolated mitochondria and peroxisomes. *J Inherited Metab Dis* 1983;6(suppl 2):123-124.
14. Trijbels JM, Monners LA, Melis G, et al: Localization of pipecolic acid metabolism in rat liver peroxisomes: Probable explanation of hyperpipecolatemia in Zellweger syndrome. *J Inherited Metab Dis* 1987;10:128-134.
15. Danpure CJ, Jennings PR: Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type 1. *FEBS Lett* 1986;201:20-24.
16. Santos MJ, Iminaka HS, Small GM, et al: Peroxisomal membrane ghosts in Zellweger syndrome: Aberrant organelle assembly. *Science* 1988;239:1536-1538.
17. Bowen P, Lee CS, Zellweger H, et al: A familial syndrome of multiple congenital defects. *Johns Hopkins Med J* 1964;114:402-414.
18. Brown FR III, Mc Adams AJ, Cummins JW, et al: Cerebro-hepato-renal (Zellweger) syndrome and neonatal adrenoleukodystrophy: Similarities in phenotype and accumulation of very long chain fatty acids. *Johns Hopkins Med J* 1982;155:344-351.
19. Jaffe R, Crumrine P, Hashida Y, et al: Neonatal adrenoleuko-dystrophy: Clinical, pathological and biochemical delineation of a syndrome affecting both males and females. *Am J Pathol* 1982;198:100-111.
20. Benke PJ, Reyes PF, Parker JC: A new form of adrenoleukodystrophy. *Hum Genet* 1981;58:204-208.
21. Zellweger H: The cerebro-hepato-renal (Zellweger) syndrome and other peroxisomal disorders. *Dev Med Child Neurol* 1987;29:821-829.
22. Poulos A, Pollard AC, Mitchell JD, et al: Patterns of Refsum's disease: Phytanic acid oxidase deficiency. *Arch Dis Child* 1984;59:222-229.
23. Budden SS, Kennaway NG, Buist NR, et al: Dysmorphic syndrome with phytanic acid oxidase deficiency, abnormal very long chain fatty acids, and pipecolic acidemia: Studies of four children. *J Pediatr* 1986;108:33-39.
24. Gilbert EF, Optiz JM, Spranger JW, et al: Chondrodysplasia punctata-rhizomelic form: Pathologic and radiologic studies on three infants. *Eur J Pediatr* 1976;123:89-109.
25. Heymans HS, Oorthyeys JW, Nelck G,

et al: Peroxisomal abnormalities in rhizomelic chrondrodysplasia punctata. *J Inherited Metab Dis* 1986;9(suppl 2):329-331.

26. Holmes RD, Wilson GN, Hajra AK: Peroxisomal enzyme deficiency in the Conradi-Hunerman form of chondrodysplasia punctata. *N Engl J Med* 1987;316:1608.

27. Ek J, Kase BF, Reith A, et al: Peroxisomal dysfunction in a boy with neurologic symptoms and amaurosis (Leber disease): Clinical and biochemical findings similar to those observed in Zellweger syndrome. *J Pediatr* 1986;108:19-24.

28. Singh I, Moser HW, Moser AB, et al: Adrenoleukodystrophy: Impaired oxidation of long chain fatty acids in cultured skin fibroblasts and adrenal cortex. *Biochem Biophys Res Commun* 1981;102:1223-1229.

29. Singh I, Moser HW, Moser AB, et al: Adrenoleukodystrophy: Impaired oxidation of very long chain fatty acids in white blood cells, cultured skin fibroblasts, and amniocytes. *Pediatr Res* 1984;18:286-290.

30. Rizzo WB, Avigan J, Chemke H, et al: Adrenoleukodystrophy: Very long-chain fatty acid metabolism in fibroblasts. *Neurology* 1984;34:163-169.

31. Tsuji S, Sano-Kawamura T, Ariga T, et al: Metabolism of [15, 16-$^3H_2$] lignoceric acid in cultured skin fibroblasts from patients with adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN). *J Neurol Sci* 1985;71:359-367.

32. Singh H, Poulos AA: A comparative study of stearic and lignoceric acid oxidation by human skin fibroblasts. *Arch Biochem Biophys* 1986;250:171-179.

33. Hashmi M, Stanley W, Singh I: Lignoceroyl-CoASH ligase–enzyme defect in fatty acid β-oxidation system in X-linked childhood adrenoleukodystrophy. *FEBS Lett* 1986;196:247-250.

34. Wanders RJA, Van Roermud CWT, Van Wigland MJA, et al: X-linked adrenoleukodystrophy: Defective peroxisomal oxidation of very long chain fatty acids but not of very long chain fatty acyl-CoA esters. *Clin Chim Acta* 1987;165:321-329.

35. Singh I, Lazo O, Stanley W, et al: Deficiency of peroxisomal lignoceryl-CoA ligase in X-linked adrenoleukodystrophy. *Fed Proc* 1988;2:256.

36. Lazo O, Contreras M, Hashmi M, et al: Peroxisomal lignoceroyl-CoA ligase in childhood adrenoleukodystrophy and adrenomyeloneuropathy. *Proc Natl Acad Sci USA*, 1988;86:7647-7651.

37. Schaumburg HH, Powers JH, Raine CS, et al: Adrenoleukodystrophy: A clinical and pathological study of 17 cases. *Arch Neurol* 1975;32:577-591.

38. Griffin JW, Goren E, Schaumberg H, et al: Adrenomyelopathy: A probable variant of adrenoleukodystrophy. *Neurology* 1977;27:1107-1113.

39. Berkovic SF, Zajac JD, Warburton DJ, et al: Adrenomyeloneuropathy: Clinical and biochemical diagnosis. *Aust NZ J Med* 1983;13:594-600.

40. Steinberg D: Phytanic acid storage disease (Refsum's disease), in Stanbury JD, Wyngaarden JB, Frederickson DS, et al (eds): *The Metabolic Basis of Inherited Disease*, ed 5. New York, McGraw-Hill International Book Co, 1983, pp 731-744.

41. Aebi HE, Wyss SR: Acatalasemia, in Stanbury JD, Wyngaarden JB, Frederickson DS (eds): *The Metabolic Basis of Inherited Disease*, ed 4. New York, McGraw-Hill International Book Co, 1978, pp 1782-1807.

42. Goldfischer S, Collins J, Rapin I, et al: Pseudo-Zellweger syndrome: Deficiencies in several peroxisomal oxidative activities. *J Pediatr* 1986;108:25-32.

43. Schram AW, Goldfischer S, Van Roermund CW, et al: Peroxisomal 3-oxoacyl-CoA thiolase deficiency: A new peroxisomal disease. *Proc Natl Acad Sci USA* 1987;84:2494-2496.

44. Kawamura N, Moser AB, Moser HW, et al: High concentration of hexacosanoate in cultured skin fibroblast lipids from adrenoleukodystrophy patients. *Biochem Biophys Res Commun* 1978;82:114-120.

45. Moser HW, Moser AB, Frayer KK, et al: Adrenoleukodystrophy: Increased plasma content of saturated very long chain fatty acids. *Neurology* 1981;31:1242-1249.

46. Nishio H, Kodama S, Yokoyama S, et al: A simple method to diagnose adrenoleukodystrophy using a dried blood spot on filter paper. *Clin Chim Acta* 1986;159:77-82.

47. Moser AB, Singh I, Brown FR III, et al: The cerebro-hepato-renal syndrome of Zellweger and neonatal adrenoleukodystrophy: Increased levels and impaired oxidation of very long chain fatty acids and prenatal diagnosis. *N Engl J Med* 1984;310:1141-1146.

48. Schutgens RB, Heymans HS, Wanders RT, et al: Prenatal diagnosis of the cerebro-hepato-renal (Zellweger) syndrome by detection of an impaired plasmalogen synthesis. *J Inherited Metab Dis* 1985;8(suppl 2):153-154.

49. Gustafsson J, Sisfontes L, Bjorkhem I: Diagnosis of Zellweger syndrome by analysis of bile acids and plasmalogens in stored dried blood collected at neonatal screening. *J Pediatr* 1987;111:264-267.

50. Gibberd FB, Billimoria JD, Page NG, et al: Heredopathia atactia polyneuritiformis (Refsum's disease) treated by diet and plasma exchange. *Lancet* 1979;1:575-578.

51. Moser HW, Tutschka PJ, Brown FR III, et al: Bone marrow transplant in adrenoleukodystrophy. *Neurology* 1984;34:1410-1417.

52. Rizzo WB, Watkins PAS, Phillips MW, et al: Adrenoleukodystrophy: Oleic acid lowers fibroblast C_{22-26} fatty acids. *Neurology* 1986;36:357-361.

53. Moser AB, Borel I, Odone A, et al: A new dietary therapy for adrenoleukodystrophy: Biochemical and preliminary clinical results in 36 patients. *Ann Neurol* 1987;21:240-249.

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ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Peripheral Neuroepithelioma in Childhood: Immunohistochemical Demonstration of Epithelial Differentiation

Masayuki Shinoda, MD; Yutaka Tsutsumi, MD; Jun-ichi Hata, MD; Seishichi Yokoyama, MD (*Arch Pathol Lab Med* 1988;112:1155-1158)

Growth Studies in Infants and Children With Down's Syndrome and Elevated Levels of Thyrotropin

Teresa Sharav, MB, BS, MPH; Roger M. Collins, Jr; Peter J. Baab, MS

• A retrospective survey of 147 patients with Down's syndrome (age range, 4 months to 27 years) showed that 60% had a thyrotropin (TSH) level higher than 5.7 mU/L in the presence of high or normal thyroxine levels. The remaining 40% of the group had low to normal TSH values. High TSH levels were predominant in patients under 4 years of age (94 children), ie, during the phase of active growth, and showed a declining trend with increasing age. All 94 infants had delayed growth of all parameters including head circumference, height, and weight, as compared with normal infants, and growth was particularly retarded in patients with TSH levels greater than 5.7 mU/L. Thyroid dysfunction, expressed as a high TSH concentration, is associated with growth retardation in children with Down's syndrome who are younger than 4 years.

(*AJDC* 1988;142:1302-1306)

The introduction of routine screening for thyroid disease in the newborn population has shown that infants with Down's syndrome have an increased incidence of thyroid dysfunction.[1] Closer examination of the data reveals mainly mild biochemical abnormalities, with some infants showing only transient hypothyroidism and other infants exhibiting decompensation. Concurrent with these findings, other studies have shown[2,3] that apart from the well-described autoimmune hypothyroidism of adolescence and postadolescence,[4-6] there is also an increased incidence of thyroid dysfunction in the infant or child with Down's syndrome. This dysfunction is expressed biochemically as an elevated thyrotropin (TSH) concentration in the presence of normal thyroxine (T_4) and triiodothyronine (T_3) values with normal thyroid antibody studies. Whether this thyroid dysfunction, which may be a compensated or an incipient hypothyroidism, has any clinical expression is of great importance.

This is a retrospective study of thyroid dysfunction in a Down's syndrome population and its implication on growth. The study focuses mainly on children with Down's syndrome who are younger than 4 years, since this is the period of most active growth.

PATIENTS AND METHODS

Patients

Patients from the Down Syndrome Clinic, W. P. Carter Center, Baltimore, were selected for the study of altered thyroid function. The age range was from 4 months to 27 years; this study focused on 94 (64%) patients younger than 4 years.

Results of thyroid studies were available for 168 home-reared patients. All patients were analyzed for chromosomal abnormalities. More than 90% of the cases were trisomy 21; the remaining cases of translocation and mosaicism were included in the study.

At the time of the initial visit, the 168 patients who were home reared and in good health were given routine T_4 and TSH analyses and were screened for the presence of antithyroglobulin and antimicrosomal, antithyroid antibodies. Hypothyroidism was present in 21 patients (T_4 value, <64 nmol/L), and either or both of the antibodies were present. These patients were older than 15 years, were considered to have autoimmune hypothyroidism, and thus were excluded from the study. In 24 of the remaining 147 patients, blood T_3 values were within normal limits; these data will not be presented herein.

Conventional, clinical laboratory procedures were used for determining the T_4 TSH, and T_3 uptake ratios.[7,8]

Statistical Analysis

Statistical analysis was performed using the Student *t* test to calculate significance and linear regression coefficients.

Growth Studies

The 94 patients younger than 4 years were subgrouped according to the blood level of TSH: patients with a TSH value greater than 5.7 mU/L (high TSH) vs those with a TSH value less than 5.7 mU/L (normal TSH). Two age-subgroups were defined: 4 months to 2 years and 2 to 4 years. The mean age of the former age group was 11.1 months for the high TSH group and 13.3 months for the normal TSH group (difference not significant). The mean age of the latter age group was 37.2 months for the high TSH group and 34.4 months for the normal TSH group (difference not significant). Growth parameter values were available in 82 children. In seven patients with Down's syndrome, one or two of the growth parameter values were not available. The deviation of growth was expressed as the fraction of normal standard deviation (SD) selected for appropriate age and sex. The mean of this fraction and its SD was calculated, and *z* test analysis was used to compare differences between groups.[9] The correlations between blood TSH and growth parameter values were studied using a computer program of polynomial regression analysis.[10] The best-fitting curve was selected according to the significance of correlation expressed as *t* value.

RESULTS

A histograph of the blood TSH concentration in 147 patients (Fig 1) shows that two populations are apparent: one in which the TSH level is higher than 5.7 mU/L (the upper limit of normal) and the other in which the TSH level is lower (designated herein as high TSH and normal TSH groups,

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Accepted for publication July 10, 1988.

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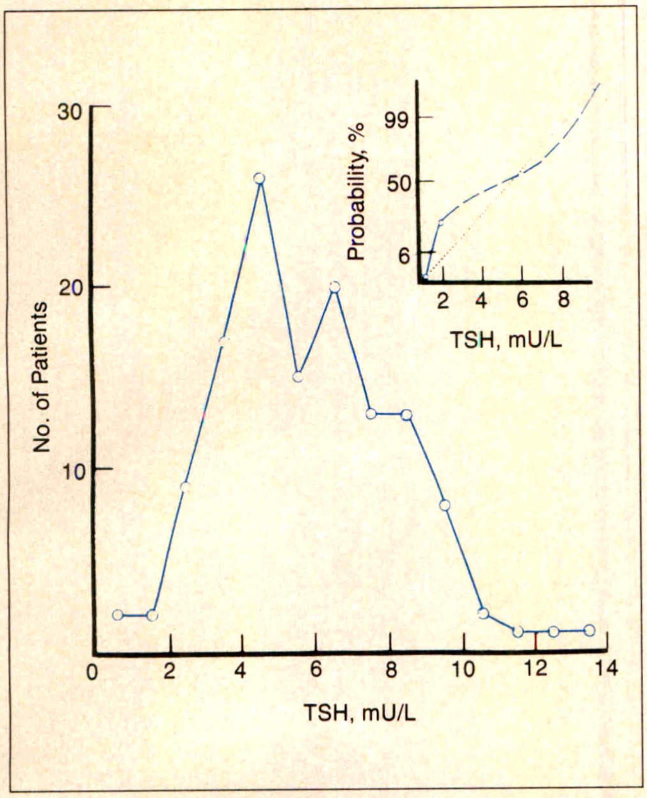

Fig 1.—Blood thyrotropin (TSH) values. Same data are plotted on probability graph (inset) and are represented by dashed line; dotted line is plot of ideal result for single population.[19] Age range of patients was from 4 months to 27 years. Each patient's value is shown once, ie, at time of initial examination.

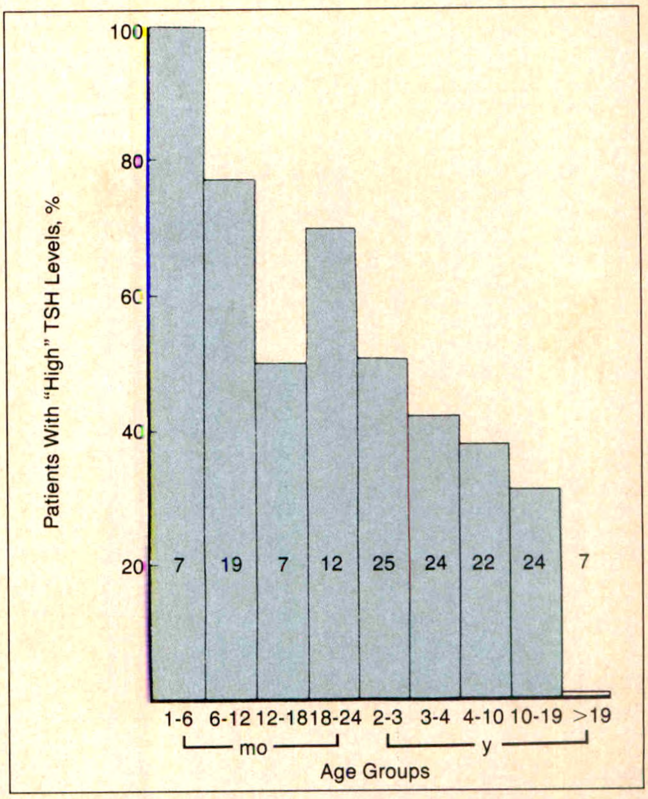

Fig 2.—Distribution of high thyrotropin (TSH) levels and thyroxine concentration in blood among various age groups. Age groups of patients in Fig 1 are shown on abscissa, and percentage of high TSH values in each group is shown on ordinate. Numbers of patients are shown within each bar.

respectively). The plot on the probability graph (Fig 1, inset) for these data is sigmoid and not linear,[11] thereby indicating the presence of two different populations each with different mean (±SD) TSH values, ie, 3.9 ± 1.1 mU/L and 8.2 ± 2.5 mU/L ($P<.001$).

The patients were arbitrarily divided into nine age groups, and the percentage of patients with high TSH values was calculated in each group (Fig 2). This value was 100% in the 4- to 6-month age group and decreased steadily until no patients could be found in the population older than 19 years.

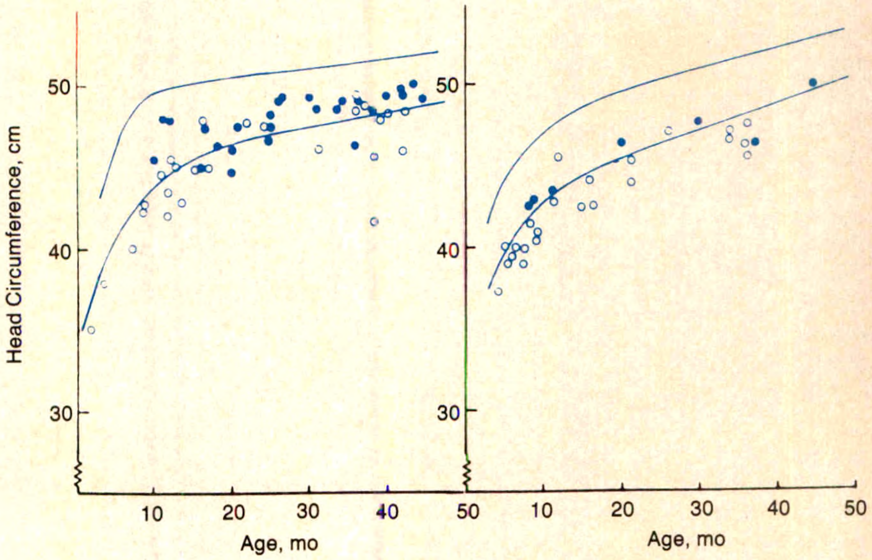

Fig 3.—Head circumference among patients with Down's syndrome. Head circumference of patients with high thyrotropin values (open circles) and of those with normal thyrotropin values (closed circles) are shown separately for male (left) and female (right) patients. Each patient's value is shown once, ie, at time of initial examination. Range of standard values, ie, fifth to 95th percentile, is indicated.[5]

Further studies focused on Down's syndrome in patients younger than 4 years since this is a period of more active growth. The T_4 values for 94 patients younger than 4 years were placed in one of the two groups according to high TSH or normal TSH values. The mean T_4 value was significantly higher among the patients with high TSH levels (143 vs 121 nmol/L; $P<.001$).

The growth of head circumference was compared between the high TSH and normal TSH groups (Fig 3) within margins of the standard fifth to 95th percentile.[12] Most patients with high

Differences of Growth Among Patients With Down's Syndrome*
Head circumference
High TSH (−2.26±1.07 mU/L) vs normal subjects
Normal TSH (−1.49±0.98 mU/L) vs normal subjects
High TSH vs normal TSH
Height
High TSH (−2.08±2.48 mU/L) vs normal subjects
Normal TSH (−1.29±0.89 mU/L) vs normal subjects
High TSH vs normal TSH
Weight
High TSH (−1.49±1.37 mU/L) vs normal subjects
Normal TSH (−0.78±1.0 mU/L) vs normal subjects
High TSH vs normal TSH

*Values are expressed as the mean ± SD. TSH indicates thyrotropin concentration. All differences are significant ($P<.05$).

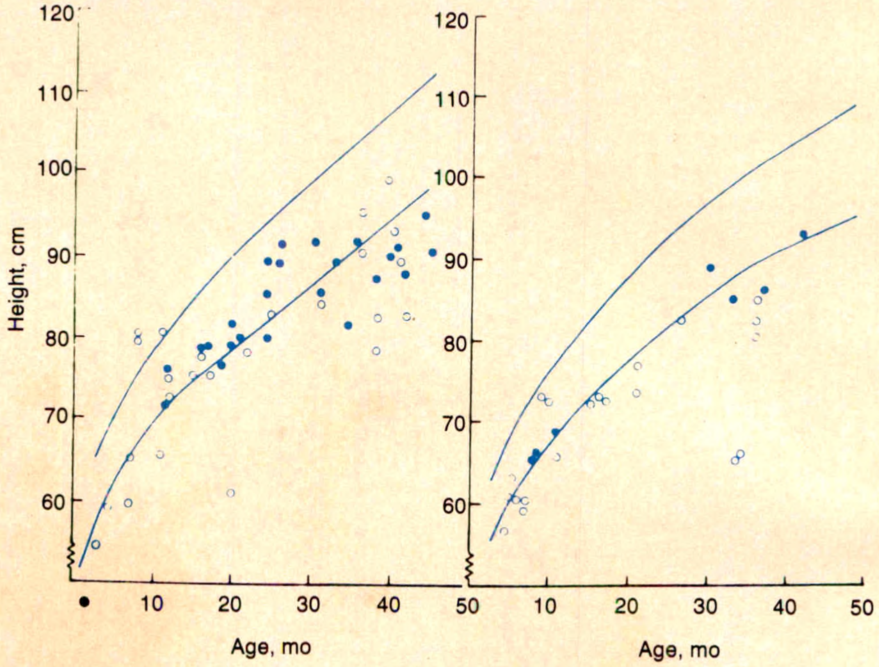

Fig 4.—Height among patients with Down's syndrome. Patients are described in Fig 3.

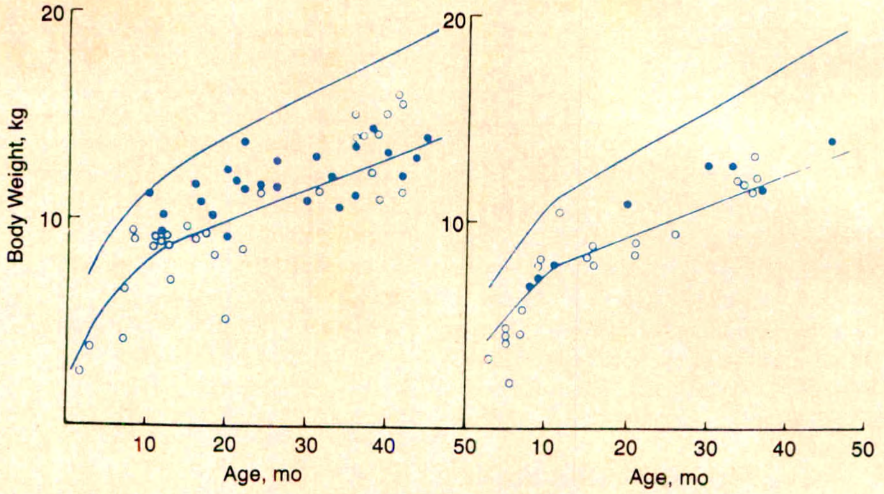

Fig 5.—Weight among patients with Down's syndrome. Patients are described in Fig 3.

TSH concentrations had head circumferences below the fifth percentile, while patients with normal TSH levels were associated with values of head circumference between the percentile limits. The deviation of head growth was expressed as the fraction of SD appropriate for age and sex (Table). The average decrement in the high TSH group was significantly greater than in either normal children or those with Down's syndrome and normal TSH values. The greatest growth of head circumference is complete by 2 years of age; therefore, the results of two age subgroups were compared. A significantly greater delay ($P<.05$) of the head circumference was observed in the 2- to 4-year age subgroup with high TSH values. In infants with Down's syndrome who were younger than 2 years, female infants had significantly smaller head circumferences than male infants ($P<.05$) (Fig 3) (Table).

The height of all patients was significantly less than normal ($P<.05$) (Fig 4) (Table). The shortness of stature was more pronounced in the high TSH group and became more accentuated with increasing age. The high TSH group always remained shorter than the normal TSH group. The retardation in growth was greatest among female patients in the 2- to 4-year age subgroup ($P<.05$).

The weight in patients with Down's syndrome was significantly less than normal (Fig 5) (Table). The slower weight gain was more pronounced in those with high TSH values. A significant difference in weight was found in the 4-month to 2-year age subgroup between the high TSH and normal TSH groups ($P<.05$).

The level of blood TSH was correlated with head circumference (Fig 6), height (Fig 7), and weight (Fig 8) in the 4-month to 2-year age subgroup. All growth parameters correlated inversely with TSH concentration. (The highly significant t values [when $t=3.79$ for $N-2=22$, $P=.001$] are indicated in individual figures.)

COMMENT

This study presents additional evidence of thyroid dysfunction, expressed as a high TSH concentration, in Down's syndrome. Two different populations with Down's syndrome were apparent, one with high TSH values and the other with normal TSH values. The high TSH group comprised mainly infants, and the number diminished after 4 years of age (Fig 2). These findings are in keeping with those of other investigators.[2,3] Two further findings were observed in the

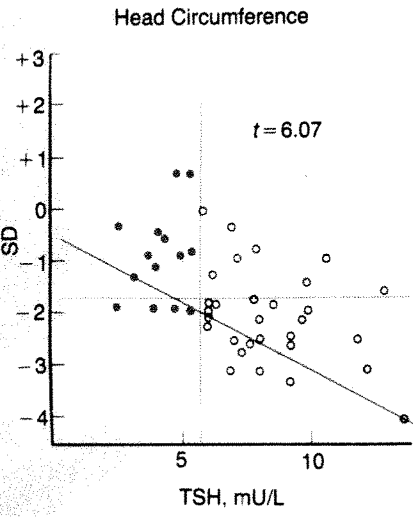

Fig 6.—Relationship between deviant growth of head circumference and blood thyrotropin (TSH) values. Patients are described in Fig 3. In each patient, retarded growth is expressed as fraction of appropriate standard deviation (SD) for age and sex; decrement (−SD) or increment (+SD) is shown on ordinate. Vertical line indicates separation between high TSH (open circles) and normal TSH (closed circles) values, while horizontal line indicates fifth percentile. Age of patients ranged from 1 month to 2 years. Orthogonal polynomial analysis indicated that best-fitting curve was a line, and *t* value was as indicated (see "Patients and Methods" section).

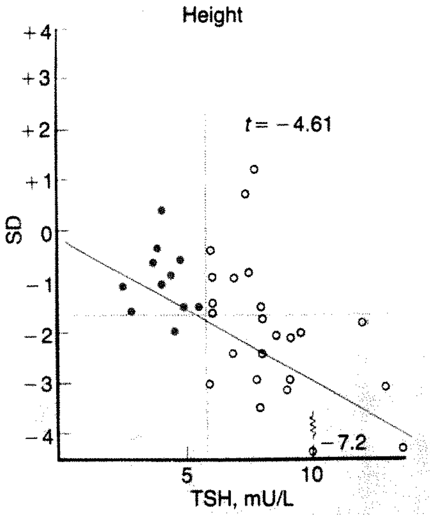

Fig 7.—Relationship between deviant growth in height and blood thyrotropin (TSH) values. Calculations and patients are described in Fig 6. Best-fitting curve was a line, and *t* value was as indicated.

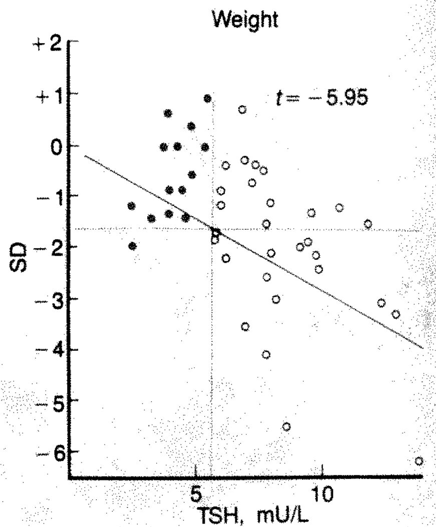

Fig 8.—Relationship between deviant growth in weight and blood thyrotropin (TSH) values. Calculations and patients are described in Fig 6. Best-fitting curve was a line, and *t* value was as indicated.

subpopulation of the 94 patients with Down's syndrome who were younger than 4 years: (1) the mean T_4 value was significantly higher ($P<.001$) in the high TSH group compared with the normal TSH group; and (2) the high TSH group showed more marked retardation of all growth parameters than did the normal TSH group (Figs 3 through 5). Correlative studies of growth parameters with levels of blood TSH show that the higher the TSH value, the greater the growth retardation (Figs 6 through 8).

It is not clear why the mean T_4 values were significantly higher among the high TSH group. Usually high TSH values are suggestive of hypothyroidism, either incipient or compensated and associated with a tendency toward low T_4 values. Physiologically, T_4 concentrations at birth are higher in the neonate, gradually declining during the first year of life to within normal adult levels.[13] The thyrotropin level is elevated in the immediate neonatal period but returns to normal by the fourth day at least. Hence, these values could be a reflection of prolongation of the normal physiologic process.

Transient hypothyroidism in the neonatal period[14] and high TSH levels up to 1 month of age have been described.[15] Many of the infants described herein presented with associated pathologic conditions, but in none of them was the TSH level elevated beyond 1 month of age.

Paradoxically, high or normal T_4 levels in the presence of high TSH values have been described in a heterogeneous group of disorders of thyroid hormone functions and have been termed *inappropriate release of TSH.*[16] Proposed causes are those of peripheral resistance to thyroid hormone or central disorders of TSH secretion. Peripheral resistance to cultured thyroid hormone has been confirmed in fibroblasts showing decreased sensitivity to thyroid hormone.[17-19] In cytologic studies of patients with Down's syndrome, cell membranes are known to have abnormal biochemical, physiologic, and receptor functions.[20,21] Whether these altered cell properties also affect thyroid hormone receptor function—though theoretically feasible—has still to be proven.

Central disorders such as hypothalamic hypopituitarism are associated with high TSH levels in the presence of normal T_4 levels.[22] Immaturity of the hypothalamic-pituitary thyroid axis in the infant with Down's syndrome could result in the secretion of immunologically competent but biologically less active TSH.[23] Other factors may come into play, such as the decrease of the pituitary threshold to T_4 with age in the feedback regulation of TSH.[24]

Furthermore, the results of the present study show that thyroid dysfunction is most apparent during the most active phase of growth, ie, during infancy. Infants with Down's syndrome who have high TSH values, despite higher T_4 values, showed marked growth retardation in all growth parameters compared with infants with normal TSH values. A greater proportion of female patients were afflicted. This finding may be related to the high incidence of hypothyroidism among females.[25]

It is not clear why infants with hypothyroidism fail to grow. One suggestion is the failure of growth hormone to act in the absence of thyroid hormone.[26] Deficiency of serum insulinlike growth factor has been described in Down's syndrome.[27]

Empirical thyroid supplementation in Down's syndrome with no biochemical evidence of thyroid disorder showed no measurable improvement in mental functioning.[28] Is a high TSH value in the presence of normal T_4 values sufficient evidence for the need of thyroid supplementation? Treatment with thyroid supplement of a number of infants with hypopituitarism and TSH deficiency led to an increased growth rate during the period of treatment.[22]

Until the cause(s) of thyroid dysfunction in Down's syndrome and the measurement of its effect on mental and physical development are clarified, there can be no rational approach to treatment.

We are grateful to Pinar Ozand, MD, PhD, for permission to study the patients under his care.

References

1. Fort P, Lifshitz F, Bellisario R, et al: Abnormalities of thyroid function in infants with Down syndrome. *J Pediatr* 1984;104:545-549.
2. Pueschel SM, Pezzullo JC: Thyroid dysfunction in Down syndrome. *AJDC* 1985;139:636-639.
3. Cutler AT, Benezra-Obeiter R, Brink SJ: Thyroid function in young children with Down syndrome. *AJDC* 1986;140:479-483.
4. Sare Z, Ruvalcaba RH, Kelly VC: Prevalence of thyroid disorder in Down syndrome. *Clin Genet* 1978;14:154-158.
5. Murdoch JC, Ratcliffe WA, McLarty DC, et al: Thyroid function in adults with Down's syndrome. *J Clin Endocrinol Metab* 1977;44:453-458.
6. Baxter RG, Larkins RG, Martin FIR: Down syndrome and thyroid function in adults. *Lancet* 1975;2:794-796.
7. Ratcliffe WA, Challand GS, Ratcliffe JG: A critical evaluation of separation methods in radioimmunoassays for total triiodothyronine and thyroxine in unextracted human serum. *Ann Clin Biochem* 1974;11:224-229.
8. Patel YC, Burger HG, Hudson B: Radioimmunoassay of serum thyrotropin: Sensitivity and specificity. *J Clin Endocrinol Metab* 1971;31:768-771.
9. Kleinbaum DG, Kupper LL: *Applied Regression Analysis and Other Multi-variable Methods.* Boston, Duxbury Press, 1978, pp 218-220.
10. Dixon WJ, Brown MB: *Biomedical Computer Programs, P-Series.* Berkeley, University of California Press, 1979.
11. Sokal RR, Rohif JF: *Graphic Methods in Biometry.* New York, WH Freeman Co, 1981, pp 117-125.
12. Hamill PVV, Drizd TA, Johnson CL, et al: Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979;32:607-629.
13. Fisher AD: Thyroid physiology and function tests in infancy and childhood, in Wemer SC, Ingbar SH (eds): *The Thyroid: A Fundamental and Clinical Text.* New York, Harper & Row Publishers Inc, 1978, pp 375-383.
14. Delange F, Dodion J, Wolter R, et al: Transient hypothyroidism in the newborn infant. *J Pediatr* 1978;92:974-976.
15. Bamasch M, Kuschnir A, Fontano O, et al: Elevated neonatal thyrotropin (TSH) values in nonhypothyroid newborns: Differentiation with congenital hypothyroids in iodine deficiency disorders and congenital hypothyroidism. Proceedings of Satellite Meeting of Ninth International Thyroid Congress in San Paulo, Brazil, 1985, pp 276-283.
16. Weintraub BD, Gershengorn MC, Kourides IA, et al: Inappropriate secretion of thyroid-stimulating hormone. *Ann Intern Med* 1981;95:339-351.
17. Smith TJ, Murata Y, Horwitz AL, et al: Regulation of glycosaminoglycan accumulation by thyroid hormone in vitro. *J Clin Invest* 1982;70:1066-1073.
18. Murata Y, Refetoff S, Horwitz AL, et al: Hormonal regulation of glycosaminoglycan accumulation in fibroblasts from patients with resistance to thyroid hormone. *J Clin Endocrinol Metab* 1983;57:1233-1239.
19. Zonefrati R, Rotella CM, Toccafondi RS, et al: Thyroid hormone receptors in human cultured fibroblasts: Evidence for cellular T_4 transport and nuclear binding. *Horm Metab Res* 1983;15:151-154.
20. Scott BS, Petit TL, Becker LE, et al: Abnormal electric membrane properties of Down's syndrome DRG neurons in cell culture. *Dev Brain Res* 1982;2:257-270.
21. McSwigan JD, Hanson DR, Lubiniecki A, et al: Down syndrome fibroblasts are hypersensitive to beta-adrenergic stimulation. *Proc Natl Acad Sci USA* 1981;78:7670-7673.
22. Gruneiro de Papendieck L, Iorcansky S, Rivarola MA, et al: Patterns of TSH response to TRH in children with hypopituitarism. *J Pediatr* 1982;100:387-392.
23. Faglia G, Bitensky L, Pinchera A, et al: Thyrotropin secretion in patients with central hypothyroidism: Evidence for reduced activity in immunoreactive thyrotropin. *J Clin Endocrinol Metab* 1979;48:989-998.
24. Letarte J, Guyda H, Dussault JH: Clinical, biochemical and radiological features of neonatal hypothyroid infants, in Burrow GN (ed): *Neonatal Thyroid Screening.* New York, Raven Press, 1980, pp 225-235.
25. Sato T, Suzuki J, Taketani T, et al: Age-related change in pituitary threshold release during thyroxin replacement therapy for cretinism. *J Clin Endocrinol Metab* 1977;44:553-559.
26. De Escobar GM, Del Rey FE: Brain damage and thyroid hormone, in Burrow GN (ed): *Neonatal Thyroid Screening.* New York, Raven Press, 1980, pp 25-49.
27. Anneren G, Sara VR, Hall K, et al: Growth and somatomedin response to growth hormone in Down's syndrome. *Arch Dis Child* 1986;61:48-52.
28. Koch R, Share J, Graliker B: The effects of cytomel on young children with Down's syndrome (mongolism): A double-blind longitudinal study. *J Pediatr* 1965;66:776-778.

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ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Prune-belly Syndrome With Prostatic Hypoplasia, Bladder Wall Rupture, and Massive Ascites in a Fetus With Trisomy

Melissa Heller Hoagland, MD; Karen A. Frank; Grover M. Hutchins, MD (*Arch Pathol Lab Med* 1988;112:1126-1128)

Behavioral Predictors of Injury in School-age Children

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• The behavior of 10 394 British children was related prospectively to their injury history between ages 5 and 10 years, obtained from parents. Aggressive and overactive behaviors at age 5 years were measured by subscales of the Rutter Child Behavior Questionnaire completed by the parents. Multivariate techniques were used to assess the association between behavior and injuries while controlling for social, demographic, and psychological characteristics. Boys' behavior at age 5 years was more strongly predictive of injuries in the subsequent five years than was girls' behavior. The odds of experiencing injuries resulting in hospitalization in boys with high aggression scores was 2.4 times that of boys with low aggression scores. The identification of high-risk children provides the foundation for understanding the behavioral mechanisms that contribute to injuries and for developing preventive strategies tailored to the needs of these children.

(*AJDC* 1988;142:1307-1312)

Several retrospective studies have identified aggression, impulsivity, and hyperactivity as correlates of childhood injuries.[1-4] It is not possible to infer from these studies whether the behaviors are causally related to the injuries because the report of behavior may be biased by the previous occurrence of the injury, because some injuries may lead to behavioral problems, and because many of the social and familial characteristics associated with problem behavior are also more common in children with injury histories.

More recently, the problem of biased recall of behavior following the occurrence of injury has been addressed by the use of prospective designs. Two prospective studies have suggested that early infant temperament characterized as "difficult" is associated with increased injury risk in the preschool period.[5,6] Injuries treated in the emergency room and motor vehicle injuries in school-age children have been found to be associated with conduct disorder[7] and with an overall measure of behavioral disturbance (I. Barry Pless, MD, Catharine Peckham, MB, Chris Power, PhD, et al, unpublished data, June 1988).

This prospective study was designed to test the following hypotheses: (1) aggressive and overactive behavior measured in early childhood contributes to the occurrence of injuries in the school-age period; (2) the association between child behavior and subsequent injury is independent of the many social and familial factors associated with injuries and problem behavior; and (3) there is a synergistic relationship between aggression and overactivity, as predicted by Mellinger and Manheimer's[8] exposure-coping model. In this theory of the injury-producing process, overactive behaviors that increase children's exposure to hazard interact with aggressive behaviors that decrease children's ability to cope with hazard. This interaction is hypothesized to produce an elevated risk of injury in children with both types of problem behavior.

SUBJECTS AND METHODS

Subjects

The subjects of these analyses were 10 394 children born in Great Britain in one week in April 1970, who were interviewed at the time of their fifth birthdays in 1975 and again at age 10 years in 1980. They were participants in a larger study, the Child Health and Education Study.[9] Of 16 004 survivors of the original birth cohort, 12 732 children and their families (79.6%) were interviewed in 1975 by home health visitors. An additional 403 children born in the same week but not in the original cohort were included in the 1975 data set. Of these 13 135 children, 1169 children (8.8%) were excluded from the injury analyses for not meeting one or more of the following criteria: mother present at the interview, family primarily English speaking, mother identifying her country of origin as the United Kingdom, child never in residential care, more than half of the behavioral data available, and singleton birth. Due to these exclusions, the results are not generalizable to children from ethnic and racial minorities in Great Britain. An additional 1572 children (11.9%) were excluded because they were missing all the injury data or because they were not interviewed in 1980. Families who were not interviewed in 1980 were somewhat more likely at the time of the five-year interview to have moved several times and to be headed by a single parent than those followed up in 1980. Children who were not followed up in 1980 did not have more injuries from birth to age 5 years, nor were they more behaviorally disturbed at age 5 years than were children who were followed up in 1980. Thus, the final sample was assumed to be more representative of a stable, settled portion of the population than of the entire population, but not biased in terms of injuries or child behavior.

Measures

Injuries.—Information about injuries was obtained through a structured interview with the parents. When the children were aged 10 years, the mothers were asked the following question:

> Since the fifth birthday, has the child had an accident requiring medical advice and treatment? Please include accidents at home, in school, on the road, and elsewhere, accidental ingestion of medicines/poisons, burns/scalds, eye injuries, near-drowning, bad cuts, and other injuries, with and without unconsciousness. If yes, please state total number of accidents.

Accepted for publication May 23, 1988.

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Table 1.—Child Behavior Subscales at Age 5 Years

Aggression	Overactivity
Destroys belongings	Restless, cannot sit still
Bullies	Squirmy, fidgety
Fights	Cannot settle
Takes things	
Disobedient	
Tells lies	
Irritable	
Temper tantrums	

Table 2.—Distribution of Children by Accident History Between Ages 5 and 10 Years by Sex*

			% With ≥1 Accidents Resulting in	
	n	% With No Injuries	Hospitalization	Ambulatory Care
Boys	5354	51.0	5.1	43.9
Girls	5040	65.2	3.4	31.4
Total	**10394**	57.9	4.3	37.9

*χ^2=214.3, *df*=2, *P*≤.001.

Details concerning the age of the child when the accident occurred, where the accident happened, the circumstances, description of injuries, place of treatment, and type of treatment were recorded for all accidents reported. Accidents resulting in more than one injury were counted only once; therefore, the frequency of injuries is equal to the frequency of reported accidents.

Children were categorized as having no injuries, one or more accidents resulting in hospitalization of one night or longer, or one or more accidents resulting in an ambulatory care visit. Children with multiple accidents resulting in injuries, some treated in the hospital and others treated on an ambulatory care basis, were classified as having an injury resulting in hospitalization.

Behavior.—In 1975, when the children were aged 5 years, the parents filled out the Rutter Child Behavior Questionnaire.[10] The responses on a random subsample of 1912 children were factor analyzed. A six-factor solution with orthogonal rotation was selected on the basis of the face validity of the item clusters. Table 1 shows the items that make up the two subscales used in these analyses, aggression and overactivity. The behavioral scales were categorized into low (≤25th percentile), medium (>25th, <90th percentile), and high (≥90th percentile).

The test-retest reliability and interrater reliability of the parent scales were assessed by the method of Rutter et al[10] and found to be 0.74 and 0.63, respectively. The validity of the scale was tested by comparing scores of the general population of 10-year-old children in the Isle of Wight with scores of children attending psychiatric clinics. Good discrimination between clinic and nonclinic children was achieved with the use of a total score of 13 or more on the behavior questionnaire, as only 15% of the boys and 8% of the girls in the general population had scores this high vs 70.8% of the boys and 66.6% of the girls who attended psychiatric clinics.

Covariates.—Seventeen characteristics of the family and child were selected as potentially confounding variables through review of the literature and from the results of our earlier study. The set of covariates to be used in the analyses was selected by subjecting all the covariates selected for consideration to an ordinary least squares stepwise regression procedure. The final set of covariates included an index of socioeconomic status consisting of the Registrar General's classification of father's occupation,[11] mother's occupation if no father figure, number of years of father's formal education, and number of years of mother's education, all standardized, summed, and set to a mean of 0 and an SD deviation of 1; an index of housing quality consisting of type of accommodation (detached house, semidetached, apartment), ownership of housing (owned, rented), the health visitor's rating of neighborhood, number of rooms, availability of garden or yard, and kitchen used for living area, summed and standardized to a mean of 0 and an SD of 1[12]; number of household moves from birth to age 5 years; number of children under age 16 years in the household; mother's full-time employment; mother's psychological well-being measured by Maternal Malaise Inventory[10]; and the number of hospitalizations not related to injury.

Data Analysis

The bivariate associations between the behaviors and injuries were tested by the Armitage χ^2 test for trend,[13] and the bivariate relationships between the covariates and behavior were assessed by one-way analyses of variance and tests of the linear component of variance.[14] Multiple regression was used to develop models, select covariates, and test interactions.[15] A significance criterion of .05 was used for all tests.

Logistic regression was used to adjust for confounding variables, calculate the odds ratios and the 95% confidence intervals (CIs), and test for linear trend.[16] Logistic regression is a standard multivariate technique used with categorical outcomes. The odds ratios derived from the logistic regression equations are the odds of experiencing one or more injuries in one group (eg, those with high aggression scores) divided by the corresponding odds in a reference group (eg, those with low aggression scores). An odds ratio of 1 indicates a lack of association. Mean values were substituted for missing data on all covariates before inclusion in the regression models. The analyses were executed through the SPSSpc+ procedures REGRESSION, ANOVA, and CROSSTABS, and the LOGIT procedure of SYSTAT.

There was one statistically significant interaction between sex and level of aggressive behavior; therefore, separate analyses were performed for each sex.

RESULTS

Boys had significantly more injuries resulting in hospitalization and injuries resulting in ambulatory care than did girls (Table 2).

Seventy-one percent of the injuries were mild (eg, sprains, strains, contusions, lacerations), 15% were fractures, 10% were head injuries resulting in fracture and/or intracranial damage, 3% were burns, and less than 1% were severe injuries such as amputations, spinal cord injuries, near-drownings, and ingestions. Boys had higher rates of head injuries, mild injuries, and miscellaneous severe injuries than girls did, while the rates of fractures, burns, and ingestions were similar in boys and girls.

Aggression and overactivity varied with the social and familial characteristics selected as potentially confounding factors (Table 3). Highly significant linear trends indicated that levels of aggression and overactivity were higher in children of low socioeconomic

Table 3.—Social and Familial Characteristics by Aggressive and Overactive Behavior at Age 5 Years (N = 10 394)

	Aggression*				Overactivity*			
	Low	Medium	High	F†	Low	Medium	High	F†
Socioeconomic status (z)‡	0.19	−0.02	−0.34	223.6§	0.17	−0.02	−0.25	139.0§
Housing Index (z)‡	0.21	−0.02	−0.28	205.1§	0.16	−0.01	−0.17	93.2§
No. of household moves, birth–5 y	0.77	0.87	0.98	43.1§	0.74	0.87	0.97	50.4§
No. of children in house	1.40	1.48	1.77	79.8§	1.58	1.45	1.49	14.0§
Mother employed full time (no, 0; yes, 1)	0.11	0.12	0.16	21.4§	0.11	0.13	0.13	3.2∥
Maternal Malaise Inventory	2.93	4.43	6.53	882.2§	3.12	4.39	6.24	606.6§
Rate of other hospitalizations/100 children¶	24.64	28.56	44.06	46.1§	24.98	28.83	40.23	29.9§

*Values given are means. Low indicates behavioral scores less than 25th percentile; medium, scores 25 percentile or higher and less than 90th percentile; and high, scores 90th percentile or higher.

†One-way analysis of variance, test of linear trend.

‡z indicates standardized scores: mean = 0; SD = 1.

§$P \leq .001$.

∥Not significant ($P > .05$).

¶Hospitalizations not related to accidental injury.

Table 4.—Distribution of Children by Injury History Between Ages 5 and 10 Years by Aggressive and Overactive Behavior at Age 5 Years

	Boys			Girls		
		% With ≥1 Injuries Resulting in			% With ≥1 Injuries Resulting in	
	n	Hospitalization	Ambulatory Care	n	Hospitalization	Ambulatory Care
Aggression*						
High	711	7.7	51.1	333	2.7	33.9
Medium	3523	5.1	44.0	3144	3.8	32.6
Low	1120	3.7	38.9	1563	2.8	28.7
χ^2†	. . .	47.6‡	38.3‡	. . .	1.1§	7.0‡
Overactivity*						
High	597	7.2	49.6	462	4.1	34.8
Medium	3645	4.9	44.2	3288	3.4	31.8
Low	1112	4.6	39.7	1290	3.1	29.2
χ^2†	. . .	18.0‡	21.7‡	. . .	2.6§	6.6∥

*Low indicates behavioral scores less than 25th percentile; medium, scores 25 percentile or higher and less than 90th percentile; and high, scores 90th percentile or higher.

†χ^2 test for linear trend, $df = 1$.

‡$P < .001$.

§Not significant ($P > .05$).

∥$P < .05$.

status and who lived in crowded and deteriorated housing, in children from families that moved frequently, in children whose mothers were employed full time and who were distressed and unhappy, and in children who had high rates of hospitalizations for causes not related to injuries.

The proportion of boys with one or more injuries resulting in hospitalization and one or more injuries resulting in an ambulatory visit increased with increasing aggression and overactivity scores at age 5 years (Table 4). Considering the aggression score as a screening test for a subsequent hospitalization for injury, the sensitivity of a high score on aggression in the boys was only 19.9%, while the specificity of having a medium or low score was 87.1%. The sensitivity of a high score on overactivity to predict hospitalization was 15.7%, and the specificity of a low or medium score was 89.1%.

There were small, statistically significant relationships between injuries treated on an ambulatory basis and both aggression and overactivity in girls, but girls' injuries resulting in hospitalization were not associated with either behavioral scale.

After control of the full set of social factors that were associated with both aggression and injuries, increasing levels of aggression continued to be associated with both types of injuries in boys (Table 5). While aggression and overactivity are interrelated, aggression in boys had an effect that was largely independent of its association with overactivity. The odds ratios decreased by less than 12% and the tests for trend remained significant at the .01 level after overactivity was controlled in addition to the other covariates.

Overactivity continued to be associated with both types of injuries in boys but not girls after control of the social factors, but the magnitude of the relationships was less than with aggression (Table 6). After the additional control of aggression, the odds ratios became indistinguishable from 1.0 and the tests of trend were not statistically significant.

None of the tests of the synergistic interaction between aggression and overactivity met the significance criterion of .05 either in the linear regression models or in the logistic regression models.

In 113 girls, aggression scores reported by their mothers were above the 90th percentile at both ages 5 and 10 years, and 250 boys had high ratings at both ages. The rates of injuries resulting in hospitalization between ages 5 and 10 years were significantly higher in these "doubly aggressive" children than in children with low ratings of aggression in both time periods (Figure). The odds ratio contrasting the odds of experiencing one or more injuries requiring hospitalization vs having no injuries in the high-scoring girls within the analogous odds in the 618 girls with low aggression scores at both time points was 3.21 (95% CI, 1.06 to 9.68). The corresponding odds ratio for the boys was 4.96 (95% CI, 2.48 to 9.95). Once all the confounding variables were controlled analytically, the odds ratio contrasting the high-scoring girls at both times vs the low-scoring girls on aggression was 1.36 (95% CI, 0.32 to 5.85), and the corresponding odds ratio for boys was 4.01 (95% CI, 1.64 to 9.82).

Table 5.—Relationship Between Injuries Between Ages 5 and 10 Years and Aggression at Age 5 Years: Unadjusted and Adjusted Odds Ratios

	Odds Ratio			
	Boys With ≥1 Injuries Resulting in		Girls With ≥1 Injuries Resulting in	
	Hospitalization	Ambulatory Care	Hospitalization	Ambulatory Care
Unadjusted				
High aggression*	2.94	1.83	1.04	1.28
Medium aggression	1.56	1.28	1.43	1.22
Low aggression†	1.00	1.00	1.00	1.00
t‡	4.88§	5.94§	1.29‖	2.93¶
Adjusted for covariates#				
High aggression*	2.42	1.70	0.71	1.16
Medium aggression	1.46	1.24	1.23	1.17
Low aggression†	1.00	1.00	1.00	1.00
t‡	3.78§	4.94§	0.08‖	1.99**

*Low indicates behavioral scores less than 25th percentile; medium, scores 25th percentile or higher and less than 90th percentile; and high, scores 90th percentile or higher.

†Reference group.

‡Test for linear trend.

§*P*<.001.

‖Not significant (*P*>.05).

¶*P*<.01.

#Adjusted for socioeconomic status, quality of housing, number of household moves, number of children, mother's employment, maternal malaise, and other hospitalizations.

***P*<.05.

We found mothers' assessments of boys' aggressive and overactive behavior at age 5 years to be predictive of the boys' injury experience in the subsequent five years. The association between aggression and injuries in boys is consistent with the results of a recent prospective study of 1295 British boys aged 6 to 8 years,[7] in which conduct disorder as rated by mothers and teachers using the Rutter questionnaires was related to the rate of boys' injuries recorded in emergency room records in the subsequent 18 months. Similarly, in a prospective analysis of the 1958 British Birth cohort, I. Barry Pless, MD, Catharine Peckham, MB, Chris Power, PhD, et al (unpublished data, June 1988) found that the boys' total Rutter score at age 7 years was associated with road traffic accidents treated in the outpatient department in the subsequent five years, but not with road traffic accidents resulting in admission to hospital. As not all of the items in the total Rutter score measure aggression or conduct disorder, the 1958 data are not directly comparable with those of the other two studies, but they do suggest that there is an association between overall behavioral disturbance and traffic accidents.

The evidence that overactivity predicts injuries is less consistent than that for aggression, as neither of the other two prospective studies (Davidson and Taylor[7] and Pless et al, unpublished data, June 1988) found a statistically significant association with overactivity in boys. The magnitude of the associations between injuries and aggression in boys was greater than with overactivity in our study, and once the association with aggression was controlled, the associations with overactivity were not statistically significant. The stronger relationship between aggression and injuries than between activity and injuries in our data and those of Davidson and Taylor[7] may reflect better measurement of aggression than overactivity, as eight items were used to define aggression vs three items for overactivity. However, an alternative explanation is that the risk-taking behavior and/or lack of impulse control associated with aggression interferes with the ability to avoid injury. This decreased ability to cope with hazard may be more salient than the increased exposure to hazard associated with high levels of motor activity.

There was no evidence in this study to support the hypothesis of an interaction between aggression and overactivity as predicted from the exposure-coping model.

The associations between aggression, overactivity, and injuries in boys were somewhat attenuated once other social and familial characteristics were controlled statistically. While better measurement of environmental hazard may have further reduced the size of the relationship, it is likely that these behaviors in boys have an effect that is independent of other social and environmental risk factors.

It is likely that the rate of injuries based on parental recall over a five-year period is an underestimate of the actual rate. However, if the underreporting is equally prevalent in parents of children with and without behavioral problems, then it should not bias the inferences about the relationship between child behavior and injuries. We attempted to assess whether this bias existed in our data by tracing the hospital records of 100 children with high levels of aggression and/or overactivity and parental reports of hospital admissions for injury, and a sample of 100 children with low or medium levels of both behaviors who also had reported admissions for injuries. Among the 76 children with aggressive and/or overactive behavior whose records could be traced, 72.4% of their reports of admissions were validated by the medical record; among the 87

Table 6.—Relationship Between Injuries Between Ages 5 and 10 Years and Overactivity at Age 5 Years: Unadjusted and Adjusted Odds Ratios

	Odds Ratio			
	Boys With ≥1 Injuries Resulting in		Girls With ≥1 Injuries Resulting in	
	Hospitalization	**Ambulatory Care**	**Hospitalization**	**Ambulatory Care**
Unadjusted				
High overactivity*	2.02	1.61	1.47	1.32
Medium overactivity	1.18	1.22	1.15	1.14
Low overactivity†	1.00	1.00	1.00	1.00
t‡	2.92§	4.47‖	1.28¶	2.52#
Adjusted for covariates**				
High overactivity*	1.81	1.47	1.11	1.20
Medium overactivity	1.15	1.16	1.03	1.08
Low overactivity†	1.00	1.00	1.00	1.00
t‡	2.37#	3.45‖	0.32¶	1.58¶

*Low indicates behavioral scores less than 25th percentile; medium, scores 25th percentile or higher and less than 90th percentile; and high, scores 90th percentile or higher.

†Reference group.

‡Test for linear trend.

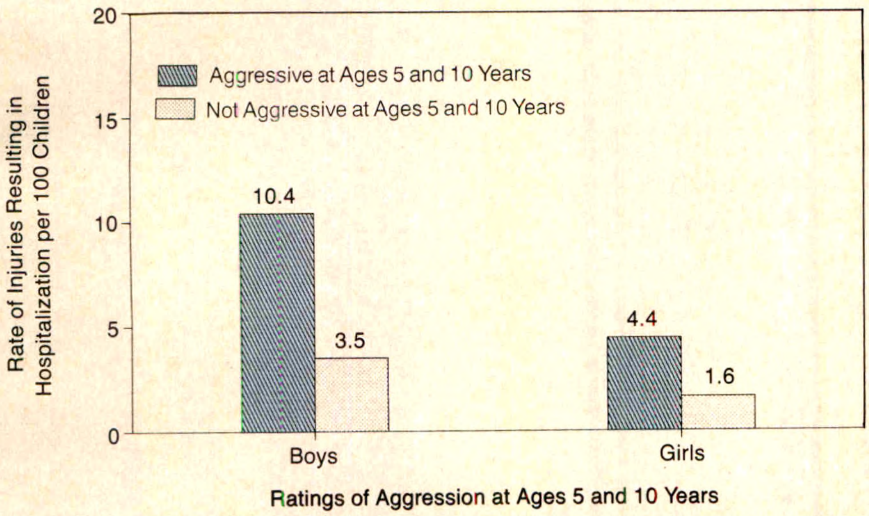
§*P*<.01.

‖*P*<.001.

¶Not significant (*P*>.05).

#*P*<.05.

**Adjusted for socioeconomic status, quality of housing, number of household moves, number of children, mother's employment, maternal malaise, and other hospitalizations.



Rate of injuries resulting in hospitalization per 100 children by ratings of aggression at ages 5 and 10 years.

children traced with lower levels of these behaviors, 79.3% of their reports were corroborated by the record review, a statistically nonsignificant difference. While these findings suggest that there may be some difference in reporting of injuries, the magnitude of the difference is not sufficiently great to account for the twofold differences in the odds of being admitted to hospital for injury observed in the boys.

Although the prospective design of this study suggests that the problem behaviors preceded the subsequent injuries in boys, the rates of injury from birth to age 5 years (measured at the same time point as the behaviors) were also significantly higher in aggressive and overactive children than in children with lower levels of these behaviors.[4] Therefore, it is possible that the observed associations between the behaviors at age 5 years and injuries from age 5 to 10 years reflect an effect of early injury on behavior and later injury. An analysis of these data, reported elsewhere, suggests that aggressiveness at age 5 years has an association with injuries from age 5 to 10 years that is independent of its association with injuries from birth to age 5 years.[17] Overactivity did not have an independent association once earlier injuries and aggression were controlled.

Girls' aggression and overactivity were only weakly associated with their subsequent injuries. Pless et al (unpublished data, June 1988) similarly did not find teachers' or mothers' ratings of girls' social adjustment and behavior at age 7 years to predict motor vehicle accidents between ages 7 and 11 years. Once the potentially confounding social and familial factors were controlled analytically in our study, only the relationship between injuries treated in ambulatory settings and aggression remained statistically significant for girls. It is possible that aggressive behavior in girls does contribute to their accident risk and that this is accurately reflected in the association between injuries resulting in ambulatory care and aggression. The lack of an observed association with injuries leading to hospitalization and aggression in girls may be due to the relatively small number of girls in the high-aggression group (n = 333) and the lower overall rate of injuries in girls. Thus, the inference that injuries requiring hospitalization are not associated with aggressive behavior in girls could be biased by the particular sample studied. The finding that girls' behavior does not predict serious injuries needs to be replicated before concluding that aggression and overactivity are not risk factors for girls. The fact that the association is weaker than it is for boys, however, is consistent with many other studies and suggests that the classification of high-risk girls may entail the identification of other characteristics that distinguish these children.

A possible explanation of the stronger relationship between injuries and behavior in boys than girls is that boys' behavior may be more stable over time than girls' behavior is. While the correlation of mothers' reports of aggressive and overactive behavior in this data set over the five years was larger for boys than girls, the magnitudes were similar (eg, aggression, .47 for boys and .42 for girls), and thus it is unlikely that a difference in stability accounts for the different associations. A second possible explanation is that the differences in girls' and boys' play activities account for the observed differences in the associations. In our sample, the girls who were aggressive at age 5 years engaged in significantly less active behaviors such as sports and bicycling than did boys with even the lowest scores on aggression. There are also several small studies that indicate that girls and boys perceive sensory stimuli differently.[18,19] Salvatore,[18] for example, found that girls overestimated the speed of oncoming vehicles and that boys underestimated the speed of the vehicles in a controlled field experiment. It may be that aggressive and overactive behaviors in girls are not important risk factors for injuries because they are coupled neither with the increased exposure to hazard of boys' play nor with a decreased ability to cope with hazard that may be perceptual.

While girls' behavior reported at age 5 years did not predict their subsequent hospitalized injuries, girls who were rated by their parents as aggressive at both ages 5 and 10 years had three times the risk of injuries resulting in hospitalization than girls who had low levels of aggression at both time points. Although it is unlikely that behavior has an independent association with hospitalized injuries in girls, persistent problem behavior in girls may be an indicator of high injury risk.

The inference that aggressive and overactive behavior in boys contributes independently to injuries occurring in the early school years is strengthened by these prospective analyses of a large, nationally representative birth cohort. The public health implication of this finding is limited by the large amount of variability of injury occurrence that is due to nonbehavioral factors, reflected by the low sensitivity of the behavioral measures. The bulk of injuries are contributed by children who cannot be defined as high risk because of their behavior; therefore, the greatest impact on the injury problem must come from community-wide efforts to provide a safer environment for all children.

The results of this study, however, lend support to the concept that certain children are less able than others to negotiate their environment safely, and this disability is due, in part, to aspects of their own behavior. If the needs of this group are to be served, effective preventive strategies need to be developed. Passive control strategies that require little or no change in individual behavior make particular sense for high-risk individuals, as children with problem behavior might be those whose individual behaviors are the most difficult to modify.[20,21] In addition, the close study of children who are at high risk because of their behavior may reveal clues to the behavioral mechanisms linking aggression to injury and thus may lead to specifically tailored behavioral interventions.

This research was supported by grants from the Department of Health and Social Security (United Kingdom), the Department of Education and Science (United Kingdom), the National Institute of Child Health and Human Development (United States), and the William T. Grant Foundation.

We gratefully acknowledge the contribution of the Regional and District Health Authorities, Health Boards, and health visitors throughout England, Scotland, and Wales and all academic staff who have previously been involved in the preparation and development of the Child Health and Education Study data sets.

References

1. Krall V: Personality characteristics of accident repeating children. *J Abnorm Soc Psychol* 1953;48:99-107.
2. Manheimer DI, Mellinger GD: Personality characteristics of the child accident repeater. *Child Dev* 1967;38:491-513.
3. Langley J, McGee R, Silva P, et al: Child behavior and accidents. *J Pediatr Psychol* 1983;8:181-189.
4. Bijur PE, Stewart-Brown S, Butler N: Child behavior and accidental injury in 11 966 preschool children. *AJDC* 1986;140:487-492.
5. Matheny AP, Brown AM, Wilson RS: Behavioral antecedents of accidental injuries in early childhood: A study of twins. *J Pediatr* 1971;79:122-124.
6. Nyman G: Infant temperament, childhood accidents, and hospitalization. *Clin Pediatr* 1987;26:398-404.
7. Davidson LL, Taylor E: Parental supervision does not explain lack of association between overactivity and childhood injuries. Read before the Ambulatory Pediatric Association 27th Annual Meeting, Anaheim, Calif, April 30, 1987.
8. Mellinger GD, Manheimer DI: An exposure-coping model of accident liability among children. *J Health Soc Behav* 1967;8:96-106.
9. Butler NR, Golding J, Howlett B: *From Birth to Five: A Study of the Health and Behaviour of Britain's Five Year Olds.* Oxford, England, Pergamon Press, 1986.
10. Rutter M, Tizard J, Whitmore K: *Education, Health and Behaviour.* London, Longman Group Ltd, 1970.
11. *Occupation Classification 1970.* London, Office of Population Censuses and Surveys, 1970.
12. Bijur PE: *The Relationship Between Child Behavior and Accidents From Birth to Five: A Multivariate Analysis of a National Cohort,* dissertation. Columbia University, New York, 1984.
13. Armitage P: Tests for linear trends in proportions and frequencies. *Biometrics* 1955;11:375-385.
14. Snedecor GW, Cochran WG: *Statistical Methods.* Ames, Iowa, Iowa State University Press, 1967.
15. Cohen J, Cohen P: *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences.* Hillsdale, NJ: Lawrence Erlbaum Assoc Inc Publishers, 1983.
16. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic Research.* Belmont, Calif, Wadsworth Inc, 1982.
17. Bijur PE, Golding J, Haslum M: Persistence of occurrence of injury: Can injuries of preschool children predict injuries of school-aged children. *Pediatrics* 1988;82:707-712.
18. Salvatore S: The ability of elementary and secondary school children to sense oncoming car velocity. *J Safety Res* 1974;6:118-125.
19. Martin G, Heimstra NW: The perception of hazard by children. *J Safety Res* 1973;5:238-246.
20. Haddon W: On the escape of tigers: An ecologic note. *Am J Public Health* 1970;60:2229-2234.
21. Withers BF, Baker SP: Epidemiology and prevention of injuries. *Emerge Med Clin North Am* 1984;2:701-715.

Platelet Vasopressin Levels in Childhood Idiopathic Nephrotic Syndrome

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• Despite the importance of disturbances in plasma volume in nephrotic patients, the only clinically accepted measurement of this value in common use is plasma renin activity. We assessed the usefulness of plasma vasopressin levels as an index of plasma volume in patients with idiopathic nephrotic syndrome. However, since 80% to 90% of arginine vasopressin circulates bound to platelets, we measured vasopressin levels in platelet-rich and platelet-poor plasma. The nephrotic patients ($n=19$) had significantly higher vasopressin levels in platelet-poor and platelet-rich plasma compared with controls (3.2±0.6 vs 1.0±0.3 pg/mL, and 10.4±3.6 vs 3.3±0.6 pg/mL, respectively). The percent binding of vasopressin to platelets was reduced in nephrotic patients compared with controls (50.2%±6% vs 70.4%±2.9%). The values for platelet-poor vasopressin, but not platelet-rich vasopressin, correlated significantly with the plasma renin activity ($r=.83$). We conclude that in nephrotic patients, platelet-poor vasopressin levels correlate with plasma renin activity and may provide a useful measure of minute-to-minute vasopressin release in response to changes in plasma volume.

(*AJDC* 1988;142:1313-1316)

Disturbances in plasma volume, due to alterations in renal sodium handling and edema formation, are an important feature of idiopathic nephrotic syndrome.[1,2] While the size of the effective extracellular fluid volume can be determined using a variety of radiolabeled molecules, these methods are less reliable in the assessment of plasma volume in patients with idiopathic nephrotic syndrome.[1] Therefore, the principal clinical index that has been employed to evaluate plasma volume in nephrotic patients has been plasma renin activity (PRA).[3,4] However, a logical alternative should be the measurement of plasma arginine vasopressin (AVP) levels, since secretion of this hormone is directly related to afferent signals that reflect the plasma volume status of patients.[5] To date, only one study has evaluated the relationship between plasma AVP concentration and the size of the effective extracellular fluid volume in nephrotic patients and it did not distinguish between platelet-rich plasma (PRP) and platelet-poor plasma (PPP).[6] Recently, it has been shown that the platelet membrane possesses a V_1-class AVP receptor, and that 85% to 90% of circulating AVP is bound to platelets.[7,8] In light of these new data, we reinvestigated the relationship between the size of the plasma volume in nephrotic children, as reflected by the PRA and AVP levels in PRP and PPP. Our results indicate a significant linear relationship between PRA and PPP AVP levels in children with idiopathic nephrotic syndrome.

SUBJECTS AND METHODS

Patients were eligible for inclusion in this study if they had idiopathic nephrotic syndrome defined by (1) proteinuria, ie, levels of urinary protein excretion exceeding 1 $g/m^2/24$ h or a urine protein-creatinine ratio greater than 2.0 in a first-voided morning specimen; (2) hypoalbuminemia, ie, serum protein levels less than 30 g/L; and (3) hypercholesterolemia. The patients were in a state of relapse, defined as proteinuria ($\geq 2+$) by results of dipstick urinalysis tests, for at least two weeks. None of the patients were clinically ill with gastrointestinal tract disease, and only one patient had such severe anasarca to warrant infusions of human albumin (25%) and furosemide infusions. The patients were not receiving corticosteroid or diuretic medications on the day of study. The control group included children seen in the nephrology clinic for nonproteinuric disorders and laboratory technology staff and volunteers.

Blood was drawn from the subjects after they had been sitting for 20 minutes, and serum samples were obtained for measurement of serum concentrations of sodium, albumin, and creatinine, osmolality, and PRA. Two additional 5-mL blood samples were drawn into separate edetic acid potassium–anticoagulated tubes. The specimens were centrifuged individually; the first tube was spun at 130 g for 20 minutes at 0°C to 4°C to obtain PRP while the second was spun at 950 g for 20 minutes at 0°C to 4°C to obtain PPP.[7] The subjects provided a urine sample for measurement of osmolality and protein-creatinine ratio.

Serum chemistry values were determined using standard methods in the clinical chemistry laboratory. The serum and urine osmolalities were measured using a vapor pressure osmometer, while urinary protein excretion was assayed using a Coomassie blue method. The PRA and AVP levels in PRP and PPP were determined using commercially available radioimmunoassay kits. The PRP AVP and PPP AVP assays each required a 2-mL sample and the intra-assay and interassay coefficients of variations were 7% and 12%, respectively.

The glomerular filtration rate was estimated from body length and serum creatinine values using standard formulas.[9,10] The platelet-associated AVP level was calculated by subtracting the PPP AVP value from the PRP AVP measurement, and the percent binding of AVP to platelets was determined by dividing the platelet-associated AVP concentration by the PRP AVP level.[7] The relationships among PRA and PRP AVP, PPP AVP, and platelet-associ-

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Accepted for publication Aug 12, 1988.

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Read in part before the 20th Annual Meeting of the American Society of Nephrology, Dec 14, 1987, Washington, DC.

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ated AVP levels were assessed using the linear regression analysis.

All results are reported as mean ± SEM. The difference in means between sample groups were evaluated using the Student *t* test. Values of $P<.05$ were considered statistically significant. This clinical study was approved by the Human Subjects Research Committee and informed consent was obtained from a parent of each child or the subject if he or she was old enough.

RESULTS

The 19 patients (12 male) with idiopathic nephrotic syndrome ranged in age from 1 to 19 years (mean, 8.5 years). The underlying diagnosis was minimal change nephrotic syndrome in ten, focal segmental glomerulosclerosis in seven, membranoproliferative glomerulonephritis in one, and congenital nephrotic syndrome in one. Nine of the 19 patients had evident edema. The mean estimated glomerular filtration rate was 105 ± 10 mL/min/1.73 m^2 and the value exceeded 90 mL/min/1.73 m^2 in all but three cases (Table 1). The seven controls (three males) had a mean age of 15.1 years, and all had a normal glomerular filtration rate. While the controls were older than the patients, age has no effect on platelet AVP levels.[7] The total platelet counts tended to be higher and the urine osmolality lower in the patients with the idiopathic nephrotic syndrome compared with controls. Serum osmolality was significantly lower in the nephrotic patients, although the mean value was within the normal range (patients with the idiopathic nephrotic syndrome vs controls, 285 ± 2 vs 290 ± 1 mmol/kg; $P<.05$). The urine protein-creatinine ratio was 15.4 ± 3.4 and the serum albumin concentration was 20 ± 2 g/L in the nephrotic patients.

The patients with idiopathic nephrotic syndrome had elevated AVP levels in PPP and PRP samples compared with controls (3.2 ± 0.6 vs 1.0 ± 0.3 pg/mL, $P<.05$; and 10.4 ± 3.6 vs 3.3 ± 0.6 pg/mL, $P<.05$, respectively) (Table 2). Based on earlier work on platelet AVP levels in adults, it is unlikely that the differences in platelet AVP levels in our patients were the consequence of the observed differences in total platelet counts.[7] The calculated platelet-associated AVP

Table 1.—Laboratory Data*

	Patients With Idiopathic Nephrotic Syndrome (n = 19)	Controls (n = 7)
Estimated GFR,† mL/min/1.73 m^2	105 ± 10	126 ± 10
Osmolality, mmol/kg		
Serum	285 ± 2	290 ± 1‡
Urine	507 ± 78	891 ± 60
Platelet counts, $\times 10^9$/L		
Total	498 ± 41	304 ± 40
Platelet-poor plasma	22 ± 4	25 ± 4

*Results are reported as mean ± SEM.

†Glomerular filtration rate (GFR) is estimated using the body length–serum creatinine formulas of Schwartz et al[9] and Schwartz and Gauthier.[10]

‡$P<.05$, controls vs patients with idiopathic nephrotic syndrome.

Table 2.—PRA and AVP Levels*

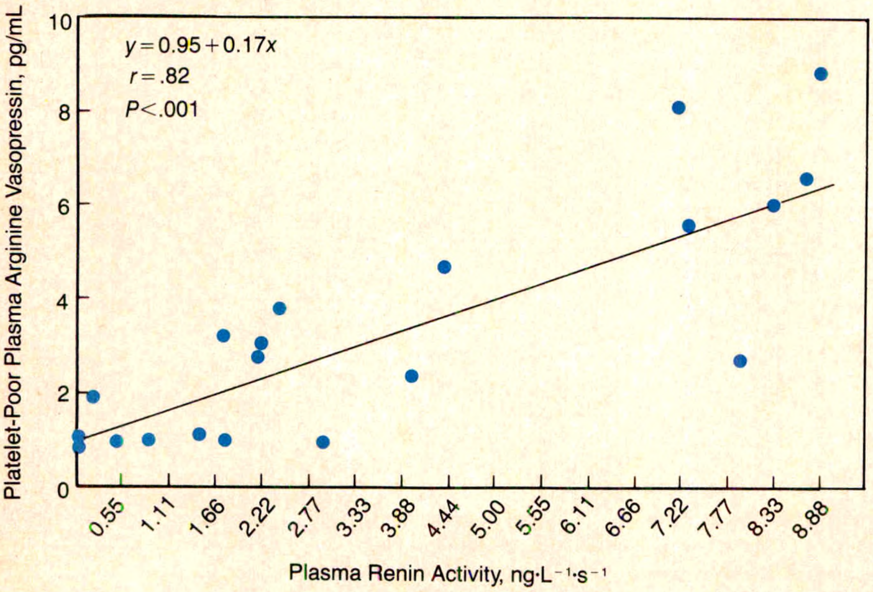
	Patients With Idiopathic Nephrotic Syndrome (n = 19)	Controls (n = 7)
PRA,† $ng \cdot L^{-1} \cdot s^{-1}$	3.63 ± 0.72	. . .
AVP, pg/mL		
Platelet-poor plasma	3.2 ± 0.6	1.0 ± 0.3‡
Platelet-rich plasma	10.4 ± 3.6	3.3 ± 0.6‡
Platelet associated	7.2 ± 3.4	2.3 ± 0.4‡
AVP binding to platelets, %	50.2 ± 6	70.4 ± 2.9‡

*Plasma renin activity (PRA) and arginine vasopressin (AVP) levels measured in patients with idiopathic nephrotic syndrome and controls. Results are reported as mean ± SEM.

†Normal range (sitting position, normal sodium diet), 0.22 to 0.61 $ng \cdot L^{-1} \cdot s^{-1}$.

‡$P<.05$, controls vs patients with idiopathic nephrotic syndrome.

Graph illustrates significant correlation between plasma renin activity and platelet-poor plasma arginine vasopressin levels in patients with idiopathic nephrotic syndrome. Circles indicate data points in individual patients.



levels were thus elevated in nephrotic patients compared with controls. In contrast, the percent binding of AVP to circulating platelets was significantly reduced in nephrotic patients (50.2% ± 6%) when compared with controls (70.4% ± 2.9%, $P<.05$). There were no significant differences in any of the measured AVP levels among those patients with or without edema. There was no significant linear relationship between the PRA and PRP AVP levels ($P>.3$) or platelet-associated AVP levels ($P>.5$) in the nephrotic patients. However, PRA was significantly correlated with the PPP AVP levels ($r=.83$, $P<.001$) (Figure). No other significant correlations between PPP AVP levels and the urine protein-creatinine ratio ($P>.2$) or serum albumin concentration ($P>.3$) were demonstrable in the patients with nephrotic syndrome.

COMMENT

In this study, we performed simultaneous measurements of PRA and PPP AVP and PRP AVP levels and have shown that there is no correlation between levels of PRP AVP or platelet-associated AVP and PRA; however, there is a highly significant correlation between the PPP AVP level and PRA. These results indicate that plasma AVP levels can be used as a clinical index to evaluate the extracellular fluid volume size in patients with idiopathic nephrotic syndrome, provided careful attention is paid to sample collection and preparation.

Certain limitations about our data should be recognized at the outset. We have not measured the blood volume of the effective plasma volume directly. Instead, we have relied on the PRA as an indirect index of the volume status in our nephrotic patients. Furthermore, while the relationship between PRA and PPP AVP levels is statistically significant, some variation in the data exists, so that while 16 of 19 PRA determinations were abnormally high, only 11 of 19 PPP AVP concentrations were elevated. Nevertheless, despite these shortcomings, we believe our conclusions are justified.

Under most circumstances, the plasma AVP concentration fluctuates in response to alterations in serum osmolality or plasma volume.[5] In all of the nephrotic patients, the serum osmolality was within the normal or low-normal range and the mean value for the group was less than that observed in the control counterparts. Thus, it is likely that the range in PPP AVP levels in the patients with idiopathic nephrotic syndrome reflects variability in the effective filling of the vascular tree. A decrease in the circulating blood volume in excess of 10% is usually considered the threshold to stimulate AVP synthesis and release.[11] Such severe volume contraction may, in fact, have been present in some of our patients. Alternatively, the relationship between plasma volume size and AVP secretion may be disturbed in patients with the syndrome, allowing increased secretion of AVP at more modest perturbations in the plasma volume. The data of Usberti et al[6] indicate that in adults with idiopathic nephrotic syndrome, there are significant inverse relationships between directly measured blood volume and plasma vasopressin levels, and PRA in the basal state. These findings support our use of the PRA as an index of the effective plasma volume in patients with idiopathic nephrotic syndrome. However, in contrast to our results, these investigators could not demonstrate a direct correlation between plasma AVP levels and PRA. It is possible that this was a consequence of their failure to discriminate between PRP AVP and PPP AVP concentrations.

There is some debate as to the accuracy and value of PRA determinations in evaluating plasma volume in nephrotic patients. Thus, contrary to the expectation that all nephrotic patients would have elevated PRA, fully 67% of adult patients have normal or low PRA.[3,4,12] In our patients with idiopathic nephrotic syndrome in nephrotic patients, 84% (16/19) did have elevated PRA. It is likely that the variability in PRA is a consequence of a summation of different mechanisms that are involved in the pathogenesis of edema in idiopathic nephrotic syndrome, ie, hypoproteinemia leading to underfilling of the vascular tree and primary renal sodium retention causing overfill of the effective extracellular fluid volume.[1,2,12,13] The wide range of PPP AVP concentrations observed in our patients, from normal to extremely elevated levels, parallels the spectrum of measured values for PRA. This indicates that the size of the plasma volume in nephrotic patients can vary significantly and lends support to this integrative hypothesis about the pathogenesis of edema in idiopathic nephrotic syndrome.

The role of the V_1-class AVP receptor on the platelet remains unclear. It is possible that the number of receptors or their binding affinity is modified by nephrotic serum milieu. This might explain the lower percent binding of AVP to platelets. Further studies will be needed to clarify these points and to determine whether the enhanced circulating free AVP concentrations result in alterations in other AVP effector mechanisms, such as blood pressure control in nephrotic patients. For example, the lower urine osmolality observed in the nephrotic patients, despite significantly higher PPP AVP levels, may be a consequence of down regulation of the vasopressin receptor in the cortical collecting tubule in the kidney.[14]

Since the half-life of circulating AVP is in the range of ten to 20 minutes,[15] the PPP AVP level represents the free AVP concentration. Therefore, it probably reflects the minute-to-minute AVP release from the posterior pituitary gland and may provide a better measure of plasma volume status at the time of clinical evaluation than simultaneously measured PRA. In contrast, the PRP determination may serve as an integrated measure of AVP secretion in response to plasma volume disturbances during the lifetime of the circulating platelets, ie, the preceding eight to ten days.[16] In this manner, the PRP AVP determination may be analogous to the hemoglobin A_{1c} measurements in diabetic patients in offering a glimpse into the recent past in evaluating the plasma volume status of patients with idiopathic nephrotic syndrome. In support of this proposal, we noted that in one patient who received an albumin and furosemide infusion for treatment of severe anasarca, there was a prompt fall in the PPP AVP level from 1.9 to less than 1.0 pg/mL and in the PRA from 0.50 to 0.05 $ng \cdot L^{-1} \cdot s^{-1}$ within three hours. During this period, the PRP AVP concentration remained essentially unchanged, ie, 4.1 pg/mL before and 3.9 pg/mL following the albumin and furosemide therapy. However, before routinely interpreting PRP AVP concentrations in the manner that we have suggested, consideration will need to be given to the confounding effects of the thrombocytosis seen in some children with minimal-change nephrotic syndrome and focal segmental glomerulosclerosis,[17] and the altered percent binding of AVP to platelets in patients with idiopathic nephrotic syndrome.

CONCLUSION

We have shown that plasma AVP levels, as a measure of plasma volume in patients with idiopathic nephrotic syndrome, correlate well with the PRA, provided the AVP determinations are done in PPP samples. The determination of platelet-associated AVP levels may supplement the information gained by measuring PRA by providing an improved clinical assessment of the volume status of nephrotic patients without the need to measure levels of 24-hour urinary sodium excretion or standardize the patient's position during blood sampling.

Gungor Karayalcin, MD, and Carol Rottendorfer performed the measurements of platelet counts in the PRP and PPP samples; and Barbara Ho provided expert assistance in the preparation of the manuscript.

References

1. Dorhout Mees EJ, Geers AB, Koomans HA: Blood volume and sodium retention in the nephrotic syndrome: A controversial pathophysiological concept. *Nephron* 1984;36:201-211.
2. Strauss J, Freundlich M, Zilleruelo G: Nephrotic edema: Etiopathogenic and therapeutic considerations. *Nephron* 1984;38:735-775.
3. Hopper J, Ryan P, Lee JC: Lipoid nephrosis in 31 adult patients. *Medicine* 1970;49:321-341.
4. Medina A, Davies D, Brown J, et al: A study of the renin-angiotensin system in the nephrotic syndrome. *Nephron* 1974;12:233-240.
5. Schrier RW, Berl T, Anderson RJ: Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979;236:F321-F333.
6. Usberti M, Federico S, Meccarello S, et al: Role of plasma vasopressin in the impairment of water excretion in nephrotic syndrome. *Kidney Int* 1984;25:422-429.
7. Preibisz JJ, Sealey JE, Laragh JH, et al: Plasma and platelet vasopressin in essential hypertension and congestive heart failure. *Hypertension* 1983;5(suppl 1):I129-I138.
8. Bichet DG, Arthus MF, Barjon JN, et al: Human platelet fraction arginine-vasopressin: Potential physiological role. *J Clin Invest* 1987;79:881-887.
9. Schwartz GJ, Haycock GB, Edelman CM Jr, et al: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58:259-266.
10. Schwartz GJ, Gauthier BG: A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr* 1985;106:522-526.
11. Baylis PH: Posterior pituitary function in health and disease. *Clin Endocrinol Metabol* 1983;12:747-770.
12. Brown EA, Markandu ND, Sagnella GA, et al: Evidence that some other mechanism other than the renin system causes sodium retention in nephrotic syndrome. *Lancet* 1982;2:1237-1240.
13. Brown EA, Markandu ND, Sagnella GA, et al: Sodium retention in nephrotic syndrome is due to an intrarenal defect: Evidence from steroid-induced remission. *Nephron* 1985;39:290-295.
14. Handelmann GE, Sayson SC: Neonatal exposure to vasopressin decreased vasopressin binding sites in the adult kidney. *Peptides* 1984;5:1217-1219.
15. Share L, Kimura T, Matsui K, et al: Metabolism of vasopressin. *Fed Proc* 1985;44:59-61.
16. Ingram GIC, Brozovic M, Slater NGP: *Bleeding Disorders: Investigation and Management*, ed 2. Boston, Blackwell Scientific Publications Inc, 1982, p 165.
17. McVicar MI, Chandra M, Margouleff D, et al: Splenic hypofunction in the nephrotic syndrome of childhood. *Am J Kidney Dis* 1986;7:395-401.

In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Upper Eyelid Crease Surgical Approach to Dermoid and Epidermoid Cysts in Children

Jan W. Kronish, MD; Richard K. Dortzbach, MD (*Arch Ophthalmol* 1988;106:1625-1627)

Danazol for Children With Immune Thrombocytopenic Purpura

Mark E. Weinblatt, MD; Joseph Kochen, MD; Jorge Ortega, MD

• Ten patients with steroid-dependent or refractory immune thrombocytopenic purpura were treated with danazol in an attempt to improve their platelet counts. Nine of the ten children exhibited an excellent initial response to the drug, with five achieving a complete, unmaintained remission. Two others were able to have their prednisone doses tapered with a resultant disappearance of steroid-induced adverse effects. No significant adverse effects of danazol were noted. Danazol seems to be effective in the treatment of children with immune thrombocytopenic purpura and would warrant additional studies to determine its proper role in the management of this common pediatric ailment.

(*AJDC* 1988;142:1317-1319)

Immune thrombocytopenic purpura (ITP), a common problem seen throughout the pediatric age range, typically presents as easy bruisability of recent onset with a low platelet count. The disorder is usually benign and self-limited with a spontaneous resolution within a period of weeks to months.

Because of the overwhelmingly good outlook for childhood ITP, controlled studies to demonstrate statistically significant differences between alternative therapies have been impossible to perform and treatment has remained controversial. Most hematologists would agree that treatment is warranted for the symptomatic, bleeding child, with corticosteroid use having, by far, the largest experience. For the child who goes on to develop a chronic form of ITP, many treatments with varying degrees of success have been in use, including steroids, splenectomy, immunosuppressive agents, vincristine sulfate, and high-dose intravenous (IV) gamma globulin.

During the past few years there has been some initial success in the treatment of adult patients with ITP using danazol, an attenuated androgen.[1-5] We report our experience with danazol therapy in several symptomatic children with refractory, steroid-dependent, and/or chronic ITP.

PATIENTS AND METHODS

Patient characteristics are presented in the Table. All children had clinical findings typical of ITP with severe thrombocytopenia and increased megakaryocytes in bone marrow. All patients were initially treated with prednisone (1.5 to 2 mg/kg/d) and either were poorly responsive or steroid dependent with hemorrhagic symptoms recurring with lowering of steroid doses. Two children, patients 1 and 8, exhibited notable adverse effects from prednisone before initiating danazol treatment; therapy was begun because of an inability to wean them from the steroids without a fall in their platelet counts and return of spontaneous hemorrhage. One child (patient 8) had an underlying autoimmune disorder with a positive fluorescent antinuclear antibody in a "speckled pattern," suggestive of a mixed connective tissue disorder. Another child (patient 9) was found to have an underlying human immunodeficiency virus infection, transmitted transplacentally from her drug-abusing mother. In addition to prednisone some patients received prior therapy that included high-dose intravenous gamma globulin, azathioprine, splenectomy, or plasmapheresis in an attempt to raise their platelet counts.

Danazol therapy was begun at a dosage of 20 to 30 mg/kg/d in divided doses and was escalated in older patients up to a maximum of 800 mg/d. Liver function tests were performed prior to beginning androgen therapy and periodically during treatment. Patients receiving concurrent prednisone therapy were weaned off of their medications after achieving a response to danazol, following which the danazol dose was also tapered, as allowed by each patient's symptoms and platelet counts. Treatment with medication was ultimately discontinued in responding patients when their platelet counts remained greater than 75×10^9/L for a period of several weeks with minimal every-other-day doses.

RESULTS

As can be seen from the Table, nine of ten patients in this trial exhibited improvement in their platelet counts after the addition of danazol. Patient response time varied from one week to one month. The platelet responses of four patients are shown in the Figure. Most patients receiving concomitant steroid therapy could be weaned off steroid treatment entirely. No liver function abnormalities or other remarkable adverse effects were noted in any of the patients. Two of the adolescents noted a mild exacerbation of preexisting acne that resolved with discontinuation of treatment with the medication. Patient 8, who experienced heavy menstrual bleeding requiring packed red blood cell transfusions before the administration of danazol, has remained amenorrheic since the addition of danazol to the steroid regimen. One patient (patient 1) responded well to danazol therapy and was able to tolerate a lower dose of alternate-day prednisone, but he could not be weaned off his medication regimen entirely and ultimately underwent a successful splenectomy. Two patients (patients 9 and 10) initially responded well to danazol therapy but rapidly became refractory; they remain thrombocytopenic despite continued treatment with gamma globulin infusions. The poorest response was seen in a child (patient 6) whose platelet count transiently rose to 35×10^9/L and whose condition has remained refractory to prednisone therapy, gamma globulin treatment, and splenectomy and remains severely thrombocytopenic.

Accepted for publication Aug 15, 1988.

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Patient Characteristics

Patient/Age at Presentation, y/Sex	Platelet Count on Presentation, $\times 10^9$/L	Platelet Response to Steroids, $\times 10^9$/L	Time to Starting Danazol Therapy, mo	Platelet Count Preceding Danazol Therapy, $\times 10^9$/L	Time to Response, wk	Platelet Response to Danazol, $\times 10^9$/L	Length of Time Receiving Danazol, mo	Outcome
1/11/M	5	424	16	62*	2	240	24	Splenectomy; platelet count >600 $\times 10^9$/L after 16 mo
2/17/M	9	56	2	17	2	176	10	Platelet count 280 $\times 10^9$/L after 38 mo with no medications
3/8/F	9	65	16	13*	2	260	24	Platelet count >200 $\times 10^9$/L after 28 mo with no medications
4/17/F	3	23	1	5*	2	124	1½	Platelet count >200 $\times 10^9$/L after 36 mo with no medications
5/14/M	4	10†	7	10*	4	360	12	Platelet count >200 $\times 10^9$/L after 36 mo with no medications
6/7/M	6	10‡	8	5*	2	35	1	Thrombocytopenic after splenectomy
7/13/M	38	59§	14	10*	1	489	4	Platelet count >425 $\times 10^9$/L after 21 mo with no medications
8/14/F	13	358‖	7	38*	1	112	13	Asymptomatic with danazol; prednisone dose tapered
9/2½/F	25	118‡	13	15*	1	124	3	Thrombocytopenic
10/9/M	9	56¶	5	20*	1	125	1½	Thrombocytopenic

*Receiving concurrent steroid therapy.

†Prior splenectomy and azathioprine therapy.

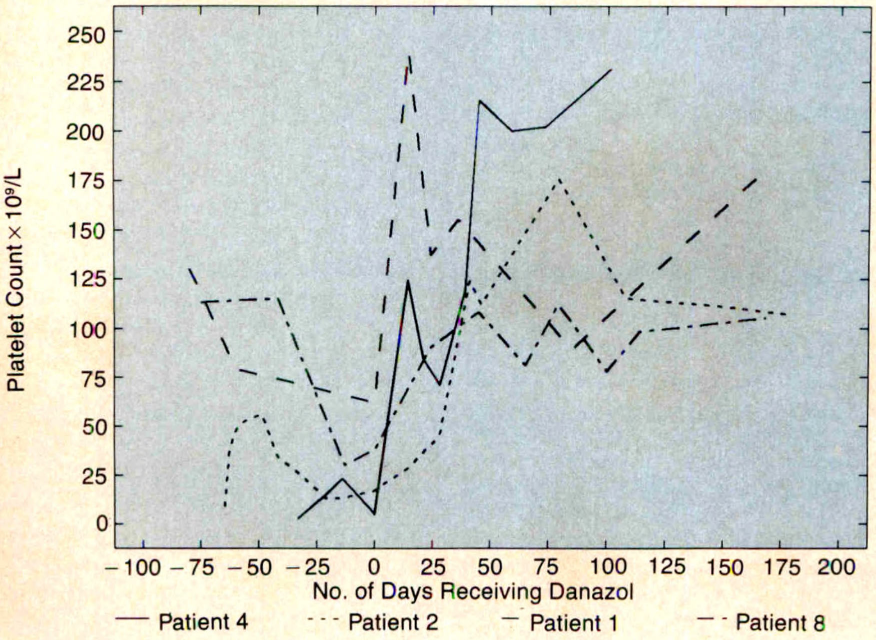
‡Prior therapy with gamma globulin.

§Prior therapy with azathioprine, gamma globulin, splenectomy, and plasmapheresis.

‖Mixed connective tissue disorder.

¶Prior gamma globulin therapy, human immunodeficiency virus.

Platelet response to danazol.



COMMENT

Immune thrombocytopenic purpura, which is a fairly common pediatric ailment, is typically uncomplicated with no serious bleeding and spontaneously resolves within a few months of onset. Patients with notable bleeding will usually respond to steroid therapy, although when and under what circumstances to use prednisone treatment remain controversial. For the refractory patient still having hemorrhagic manifestations, many therapies have been used over the years with splenectomy being the most widely used and successful treatment.[4,6,7]

In hopes of avoiding splenectomy with the inherent risk of overwhelming sepsis from encapsulated organisms, several different medical treatments are used. One of the most recent therapies that has received much attention is that of high-dose IV gamma globulin.[8-11] The presumed mechanism of action is a competitive block of the site of uptake of the antibody-bound platelet by gamma globulins.[6,8,9] After some initial enthusiasm for this approach, we and others have found this treatment not to be as effective as hoped; the conditions of most patients suffering from chronic ITP ultimately become refractory to this treatment and many steroid nonresponders show no benefit from the infusions.[12,13] One large randomized study showed no advantages of high-dose IV gamma globulin over prednisone for acute ITP.[12,14] In addition, increasing reports of adverse effects such as fever, headaches, fatal thrombosis,[15] hemolysis,[16,17] and transmission of non-A, non-B hepatitis[18,19] have shown this treatment to be far from benign. Finally, the expense of high-dose IV gamma globulin therapy as well as the need for IV infusion has made this type of treatment less acceptable for many children and their families. Other therapies used over the years, including a variety of immunosuppressive agents (such as azathioprine and cyclophosphamide) and other cytotoxic medications (vincristine and colchicine), have fallen into disfavor because of a lack of efficacy, and this has stimulated a search for newer treatments that might be able to avoid splenectomy. Cyclosporine has had limited success in some patients,[20] and more recently, the use of IV $Rh_o(D)$ immune globulin has shown promise in refractory patients and is undergoing clinical trials.[21,22]

Danazol, an attenuated androgen, has recently received attention for treatment of a number of disorders, including hemophilia A[23,24] and autoimmune hemolytic anemia.[25] There have been several reports of improvement in platelet counts in adults with chronic ITP.[1-5] The presumed mechanism of improvement is through a decrease in the number of monocyte-binding sites for monomeric IgG (Fc receptors) that decreases the number of binding sites for antibody-bound platelets and, thus, their removal from the vascular system.[3] Another hypothesis is that the improvement in platelet counts is mediated by a restoration of suppressor T-cell function and a subsequent decrease in antibody production,[26,27] although Schreiber et al[3] found no notable change in the level of platelet-associated IgG. In addition, danazol binds to steroid-binding globulin, thereby displacing and freeing active hormones, enhancing their access to other tissues. This could account for the synergistic action of glucocorticoids and danazol observed in our patients, as well as those of Ahn et al.[1]

In the absence of any well-controlled study of therapy for refractory, steroid-dependent, or chronic childhood ITP, there will continue to be controversy and confusion regarding the best mode of individualized treatment for the patient. While our approach is still conservative in nature, initially administering prednisone because of its long history of safety and efficacy, for patients who are steroid dependent or who fail to respond and are symptomatic (usually with platelet counts $<35 \times 10^9$/L), we would only then seek to use an alternative therapy. Our promising results in this small group of patients, coupled with the lack of notable adverse effects of danazol, would make this an attractive addition to the therapeutic choices available for ITP. Prospective studies comparing the relative cost-effectiveness of danazol vs high-dose gamma globulin or splenectomy will be necessary to help clarify the future role of this treatment.

Jeffrey Lipton, MD, Chief of Pediatric Hematology at Mount Sinai Hospital, New York, and Philip Scimeca, MD, contributed patients for this study.

References

1. Ahn YS, Harrington WJ, Simon SR, et al: Danazol for the treatment of idiopathic thrombocytopenic purpura. *N Engl J Med* 1983;308:1396-1399.
2. Ahn YS, Mylvaganam R, Garcia RO, et al: Low-dose danazol therapy in idiopathic thrombocytopenic purpura. *Ann Intern Med* 1987;107:177-181.
3. Schreiber AD, Chien AD, Tomaski A, et al: Effect of danazol in immune thrombocytopenic purpura. *N Engl J Med* 1987;316:503-508
4. Harrington WJ, Ahn YS, Byrnes JJ, et al: Treatment of idiopathic thrombocytopenic purpura. *Hosp Pract Off* 1983;18:205-220.
5. McVerry BA, Auger M, Bellingham AJ: The use of danazol in the management of chronic immune thrombocytopenic purpura. *Br J Haematol* 1985;61:145-148.
6. Schulman I: Idiopathic (immune) thrombocytopenic purpura in children: Pathogenesis and treatment. *Pediatr Rev* 1983;5:173-178.
7. Lilleyman JS: Management of childhood idiopathic thrombocytopenic purpura. *Br J Haematol* 1983;54:11-14.
8. Imbach P, Barandun S, d'Apuzzo V, et al: High-dose intravenous gamma globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1:1228-1231.
9. Fehr J, Hofman V, Kappeler U: Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med* 1982;306:1254-1258.
10. Bussel JB, Schulman I, Hilgartner MW, et al: Intravenous use of gamma globulin in the treatment of chronic immune thrombocytopenic purpura as a means to defer splenectomy. *J Pediatr* 1983;103:651-654.
11. Bussel JB, Goldman A, Imbach P, et al: Treatment of acute idiopathic thrombocytopenia of childhood with intravenous infusions of gamma globulin. *J Pediatr* 1985;106:886-890.
12. Imbach P, Wagner HP, Berchtold W, et al: Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985;2:464-468.
13. Warrier IA, Lusher JM: Intravenous gamma globulin (Gamimune) for treatment of chronic idiopathic thrombocytopenic purpura (ITP). *Am J Hematol* 1986;23:323-328.
14. Walker RW, Walker W: Intravenous immunoglobulin for autoimmune thrombocytopenia of childhood. *Lancet* 1985;2:1011.
15. Woodruff RK, Grigg AP, Firkin FC, et al: Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986;2:217-218.
16. Nakamura S, Yoshida T, Ohtake S, et al: Hemolysis due to high-dose intravenous gamma globulin treatment for patients with idiopathic thrombocytopenic purpura. *Acta Haematol* 1986;76:115-118.
17. Whitsett CF, Pierce JA, Daffin LE: Positive direct antiglobulin tests associated with intravenous gamma globulin use in bone marrow transplant recipients. *Transplantation* 1986;41:663-664.
18. Lever AML, Webster ADB, Brown D, et al: Non-A, non-B hepatitis after intravenous gamma globulin. *Lancet* 1985;1:587.
19. Trepo C, Hantz O, Vitvitski L: Non-A, non-B hepatitis after intravenous gamma globulin. *Lancet* 1986;1:322.
20. Velu TJ: Cyclosporine for the treatment of refractory idiopathic thrombocytopenic purpura. *Eur J Haematol* 1987;38:95.
21. Salama A, Mueller-Eckhardt C, Kiefel V: Effect of intravenous immunoglobulin in immune thrombocytopenia. *Lancet* 1983;2:193-195.
22. Baglin TP, Smith MP, Boughton BJ: Rapid and complete response of immune thrombocytopenic purpura to a single injection of rhesus anti-D immunoglobulin. *Lancet* 1986;1:1329-1330.
23. Saidi P, Lega BZ, Kim HC, et al: Effect of danazol on clotting factor levels, bleeding incidence, factor infusion requirements, and immune parameters in hemophilia. *Blood* 1986;68:673-679.
24. Kasper CK, Boylen AL: Poor response to danazol in hemophilia. *Blood* 1985;65:211-213.
25. Ahn YS, Harrington WJ, Mylvaganam R, et al: Danazol therapy in autoimmune hemolytic anemia (AIHA), abstracted. *Blood* 1983;62(suppl):102a.
26. Eidinger D, Garrett TJ: Studies of the regulatory effects of the sex hormones on antibody formation and stem cell differentiation. *J Exp Med* 1972;136:1098-1116.
27. Ahn YS, Harrington WJ, Mylvaganam R, et al: Danazol therapy restores helper/suppressor (T4/T8) ratios in patients with idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA), abstracted. *Blood* 1983;62(suppl):241a.

ECMO: Regional Evaluation of Need and Applicability of Selection Criteria

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• The need and indications for neonatal extracorporeal membrane oxygenation (ECMO) are controversial. The need for ECMO in two New England states was studied through a review of deaths due to respiratory failure in near- and full-term infants. Vermont averaged 2.4 and Maine averaged 7.4 deaths annually. Neither state demonstrated sufficient respiratory deaths to establish ECMO capability. The number of "potential" ECMO candidates, based on published selection criteria, was studied, and the applicability of criteria was evaluated. A two-year review revealed 16 potential candidates from Maine and 19 from Vermont. No criterion accurately identified nonsurvivors of conventional ventilatory therapy. Only one criterion in one institution demonstrated an association with chronic lung disease. The data demonstrated that published ECMO selection criteria were not applicable in different populations.

(*AJDC* 1988;142:1320-1324)

Extracorporeal membrane oxygenation (ECMO) is a technique of extrathoracic cardiopulmonary bypass utilized in the treatment of severe respiratory failure in near- and full-term neonates whose conditions are not improving with maximal medical and conventional ventilatory therapy. The enthusiasm for ECMO has evolved based on collected experiences and survival statistics since its introduction for use in neonates in 1975.[1-5] As of June 1988, 49 medical centers have established ECMO programs. Among 1610 patients treated with ECMO, the survival rate is reported to be 82%.[6]

Respectful criticism is directed at the fact that ECMO has been widely accepted before rigorous, prospective, scientific scrutiny addressing the need, indications, efficacy, and sequelae.[7-20] The only published prospective, randomized trial[3] has been subject to much criticism.[7,8] The real need for ECMO may, in fact, be less than the perceived need.

We conducted an ECMO feasibility study in two northern New England states (Vermont and Maine). The three purposes of this retrospective study were (1) to assess the need for ECMO within the two states; (2) to determine the number of "potential" ECMO candidates from each state's tertiary intensive care nursery (ICN) (Medical Center Hospital of Vermont [MCHV], Burlington, and Maine Medical Center [MMC], Portland) based on published ECMO patient selection criteria[1,3,5,21]; and (3) to evaluate the ability of published ECMO criteria to identify accurately the patient who would not survive conventional ventilatory management or the patient who would develop chronic lung disease within the patient population of MCHV and MMC.

METHODS AND PATIENT SELECTION

Determining Regional Need for ECMO

The need for ECMO in each state was determined in terms of the occurrence of neonatal deaths due to respiratory failure in near- (>34 weeks' gestation) and full-term infants. Neonatal deaths due to respiratory failure provided an index as to the number of patients who failed conventional therapy within each of the two states. The data were obtained through linked birth-death vital statistic records of the states of Maine and Vermont from 1981 through 1985. From these data, we computed the average annual death rate due to respiratory failure for this population of neonates in each of the two states.

Determining Number of Potential ECMO Candidates

We reviewed the charts of all patients admitted to each of the two tertiary ICNs. From this two-year retrospective review, we chose subjects according to the eligibility and exclusion criteria in Table 1. These criteria are generally accepted among many ECMO centers.[1-3,22-25]

A patient qualified as a potential ECMO candidate if the patient met at least one of six specific ECMO respiratory criteria *after* requiring maximal conventional ventilatory therapy during the first six days of life (Table 2). The six selected ECMO criteria are a collection of criteria from two of the largest ECMO centers in the United States.[1,3,5,21]

A patient was considered to receive maximal conventional therapy if he/she required at least a fraction of inspired oxygen of 1.00 and intermittent mandatory ventilation (IMV) of 60 breaths/min.

Assessment of ECMO Respiratory Selection Criteria to Identify Accurately Nonsurvivors or Survivors With Chronic Lung Disease

Each potential ECMO candidate was assessed with respect to outcome (specifically death or chronic lung disease) while he/she was managed with maximal conventional ventilatory support. Each ECMO respiratory selection criterion was individually evaluated with respect to its association with survival vs mortality and chronic lung disease vs no chronic lung disease. Chronic lung disease was defined as a requirement for supplemental oxygen for 28 days or more since birth. We used the two-tailed Fisher's exact test to analyze the data statistically.

Accepted for publication Aug 12, 1988.

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Presented at the Ross Laboratories Special Conference: Two Great Debates in Neonatology, Washington, DC, Dec 7, 1987, and at the Poster Session, Society of Pediatric Research, Washington, DC, May 3, 1988.

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Table 1.—ECMO Study Patient Selection*

Patient Selection Criteria
Eligibility criteria
Birth weight, >2 kg; gestational age, >34 wk
Postnatal age, <7 d
Respiratory failure requiring maximal ventilatory assistance (Fio$_2$ = 1.00; IMV >60 breaths/min)
Exclusion criteria
Any chromosomal, congenital, or central nervous system abnormalities incompatible with life
Evidence of any major coagulopathy
Evidence of intracranial hemorrhage more extensive than subependymal hemorrhage

*ECMO indicates extracorporeal membrane oxygenation; Fio$_2$, fraction of inspired oxygen; and IMV, intermittent mandatory ventilation.

Table 2.—ECMO Respiratory Selection Criteria*

Respiratory Selection Criteria
Acute deterioration: Pao$_2$, <40 mm Hg × 2 h and/or pH <7.15 × 2 h
Unresponsiveness: Pao$_2$, <55 mm Hg and pH <7.4 × 3 h
Barotrauma (any 4 of 7 indications simultaneously):
Pulmonary interstitial emphysema
Pneumothorax
Pneumomediastinum
Pneumoperitoneum
Subcutaneous emphysema
Persistent air leak × 24 h
MAP, >15 cm H_2O
AaDo$_2$: either ≥610 × 8 consecutive h or ≥605 × 4 consecutive h with PIP ≥38 cm H_2O
{AaDo$_2$ = 713 × Fio$_2$ − Paco$_2$/R + [Paco$_2$ × Fio$_2$ × (1 − R)/R] − Pao$_2$}
Diaphragmatic hernia: Pao$_2$, <80 mm Hg on Fio$_2$, >0.8, after honeymoon period
OI (MAP × Fio$_2$ × 100/postductal Pao$_2$)
OI, >25<40
OI ≥40

*Data adapted from Ortiz et al,[1] Bartlett et al,[3] and Miller et al.[5] ECMO indicates extracorporeal membrane oxygenation; Pao$_2$, arterial oxygen pressure; MAP, mean airway pressure; AaDo$_2$, alveolar-arterial oxygen gradient; PIP, peak inspiratory pressure; Fio$_2$, fraction of inspired oxygen; Paco$_2$, arterial carbon dioxide pressure; R, respiratory quotient; and OI, oxygenation index.

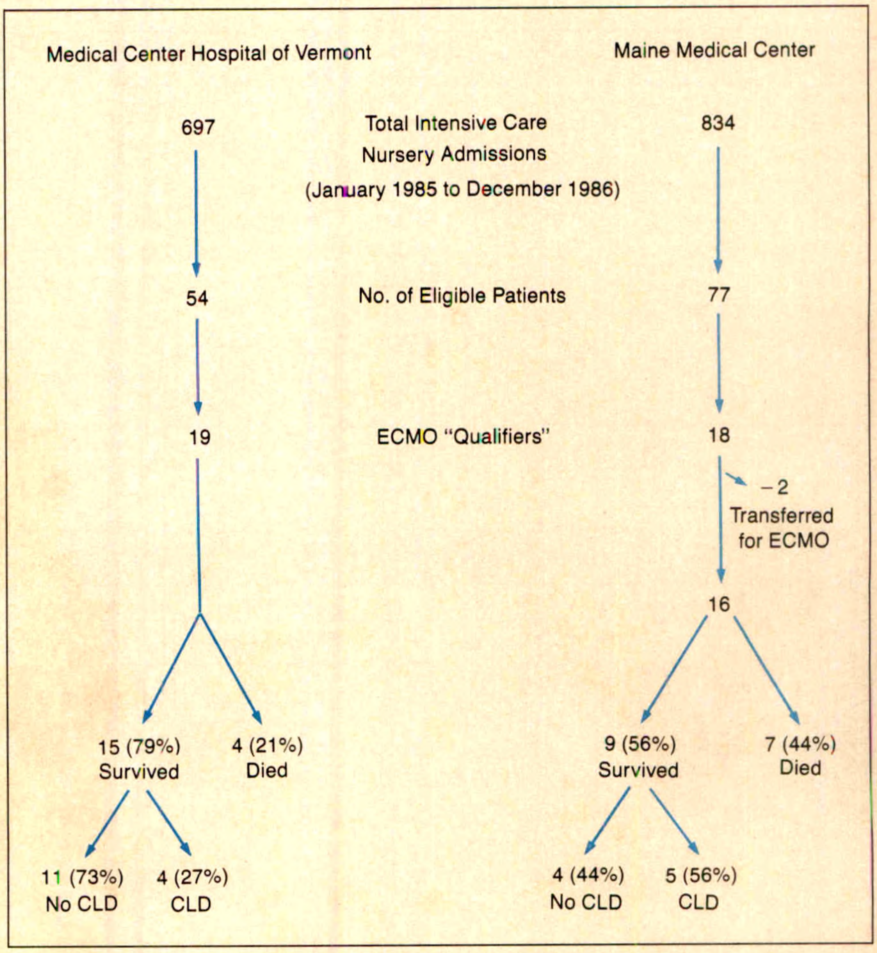
RESULTS

Need for ECMO in States of Vermont and Maine

Thirty-seven and 12 resident neonatal deaths due to respiratory failure in near- or full-term infants occurred in Maine and Vermont, respectively, from 1981 through 1985. This was an annual average of 7.4 (Maine) and 2.4 (Vermont) deaths for this five-year period. The average annual death rate due to respiratory deaths in infants greater than 34 weeks' gestation was 0.3 deaths per 1000 livebirths in Vermont and 0.5 deaths per 1000 livebirths in Maine.

Potential ECMO Candidates at MCHV and MMC

Fifty-four of 697 total ICN admissions to MCHV and 77 of 834 total ICN admissions from MMC met our inclusion criteria for the study. During the two-year study period, 19 of 54 study subjects from MCHV and 18 of 77 study subjects from MMC met at least one ECMO respiratory criterion after requiring maximal conventional ventilation during the first six days of life. Therefore, during the two-year period, the published ECMO respiratory criteria identified an average nine to ten patients per year in each medical center who would theoretically qualify as ECMO candidates (Figure).



Outcome of eligible patients. ECMO indicates extracorporeal membrane oxygenation; CLD, chronic lung disease.

Outcome of ECMO Candidates and Applicability of ECMO Criteria

Fifteen (79%) of 19 ECMO candidates from MCHV survived with maximal conventional ventilation. Eleven (73%) of the 15 survivors had no chronic lung disease. Sixteen of 18 patients from MMC were managed solely with maximal conventional ventilatory therapy. Nine (56%) of the 16 patients survived, and four (44%) of the nine survived without chronic lung disease. Two of the 18 MMC ECMO candidates (both with congenital dia-

Table 3.—MCHV Association of Individual ECMO Criteria With Survival/Mortality*

ECMO Criteria	n	Met Criteria: Survived	Met Criteria: Died	Did Not Meet Criteria: Survived	Did Not Meet Criteria: Died	P†
Acute deterioration	19	7/8 (87.5)	1/8 (12.5)	8/11 (72.7)	3/11 (27.3)	.60
Unresponsiveness	19	11/12 (91.7)	1/12 (8.3)	4/7 (57.1)	3/7 (42.9)	.12
Barotrauma	19	1/3 (33.3)	2/3 (66.7)	14/16 (87.5)	2/16 (12.5)	.10
AaDo$_2$ (≥610 × 8 h or ≥605 × 4 h [with PIP ≥38 cm H$_2$O])	19	8/11 (72.7)	3/11 (27.3)	7/8 (87.5)	1/8 (12.5)	.60
Diaphragmatic hernia	1	0/1 (0)	1/1 (100)	0/0 (0)	0/0 (0)	. . .
Oxygenation index						
>25<40	19	2/3 (66.7)	1/3 (33.3)	13/16 (81.3)	3/16 (18.8)	1.00
≥40	19	11/14 (78.6)	3/14 (21.4)	4/5 (80.0)	1/5 (20.0)	1.00

No. (%) of Patients

*MCHV indicates Medical Center Hospital of Vermont; ECMO, extracorporeal membrane oxygenation; AaDo$_2$, alveolar-arterial oxygen gradient; and PIP, peak inspiratory pressure.

†Two-tailed Fisher's exact test.

Table 4.—MMC Association of Individual ECMO Criteria With Survival/Mortality*

ECMO Criteria	n	Met Criteria: Survived	Met Criteria: Died	Did Not Meet Criteria: Survived	Did Not Meet Criteria: Died	P†
Acute deterioration	16	4/10 (40)	6/10 (60)	5/6 (83.3)	1/6 (16.7)	.15
Unresponsiveness	16	6/9 (66.7)	3/9 (33.3)	3/7 (42.9)	4/7 (57.1)	.61
Barotrauma	16	3/4 (75)	1/4 (25)	6/12 (50)	6/12 (50)	.58
AaDo$_2$ (≥610 × 8 h or ≥605 × 4 h [with PIP ≥38 cm H$_2$O])	16	8/15 (53.3)	7/15 (46.7)	1/1 (100)	0/1 (0)	1.00
Diaphragmatic hernia	2	0/2 (0)	2/2 (100)	0/0 (0)	0/0 (0)	. . .

No. (%) of Patients

*MMC indicates Maine Medical Center; EMCO, extracorporeal membrane oxygenation; AaDo$_2$, alveolar-arterial oxygen gradient; and PIP, peak inspiratory pressure.

†Two-tailed Fisher's exact test.

Table 5.—MCHV Association of Individual ECMO Criteria With CLD*

ECMO Criteria	n	Met Criteria: No CLD	Met Criteria: CLD	Did Not Meet Criteria: No CLD	Did Not Meet Criteria: CLD	P†
Acute deterioration	16	6/7 (85.7)	1/7 (14.3)	5/9 (55.6)	4/9 (44.4)	.31
Unresponsiveness	16	8/11 (72.7)	3/11 (27.3)	3/5 (60.0)	2/5 (40.0)	1.00
Barotrauma	16	1/2 (50.0)	1/2 (50.0)	10/14 (71.4)	4/14 (28.6)	1.00
AaDo$_2$ (≥610 × 8 h or ≥605 × 4 h [with PIP ≥38 cm H$_2$O])	16	6/9 (66.7)	3/9 (33.3)	5/7 (71.4)	2/7 (28.6)	1.00
Oxygenation index						
>25<40	16	1/2 (50.0)	1/2 (50.0)	10/14 (71.4)	4/14 (28.6)	1.00
≥40	16	8/12 (66.7)	4/12 (33.3)	3/4 (75.0)	1/4 (25.0)	. . .

No. (%) of Patients

*MCHV indicates Medical Center Hospital of Vermont; ECMO, extracorporeal membrane oxygenation; CLD, chronic lung disease; AaDo$_2$, alveolar-arterial oxygen gradient; PIP, peak inspiratory pressure.

†Two-tailed Fisher's exact test.

phragmatic hernia) were referred for ECMO therapy to another medical center. One of the two survived ECMO intervention (Figure). These two candidates were excluded from the final analysis as they received therapy other than maximal conventional ventilatory therapy.

Among the 19 ECMO candidates from MCHV, 11 (58%) had no adverse outcome (ie, death or chronic lung disease) with conventional ventilatory management. Among the 16 ECMO candidates from MMC managed with conventional ventilation, four (25%) had no adverse outcome. Therefore, based on published criteria, 15 (43%) of 35 ECMO "qualifiers" survived maximal conventional therapy without chronic lung disease and without ECMO in these two populations. Combined mortality and chronic lung disease data indicate that MMC and MCHV may each have four to six ECMO candidates annually.

With respect to the applicability of ECMO respiratory criteria, none of the criteria were able to discriminate effectively between survivors and nonsurvivors in either medical center (Tables 3 and 4). At MMC, only one of the ECMO respiratory criteria (ie, arterial oxygen pressure, <55 mm Hg, and pH, <7.4, for three hours) revealed a statistically significant association ($P = .05$) with the eventual development of chronic lung disease. None of the remaining ECMO criteria at MMC and none of the criteria at MCHV were significant in discriminating between patients who developed chronic lung disease from those without chronic lung disease (Tables 5 and 6).

COMMENT

The need and indications for ECMO are controversial. Current recommendations suggest that an ECMO center treat a minimum of ten patients yearly to maintain technical expertise.[21] This ECMO feasibility study demonstrated that neither state nor medical center had a sufficient number of fatal respiratory failures in near- or full-term infants to warrant the establishment of individual ECMO programs.

The other conclusion of our study is that none of the published ECMO respiratory selection criteria evaluated in this review were applicable to either neonatal population. Only one criterion in one institution demonstrated an association with chronic lung disease. The criterion of an alveolar-arterial oxygen gradient (AaDo$_2$) of 605 or greater for four hours with a

Table 6.—MMC Association of Individual ECMO Criteria With CLD*

		No. (%) of Patients				
		Met Criteria		Did Not Meet Criteria		
ECMO Criteria	n	No CLD	CLD	No CLD	CLD	P†
Acute deterioration	9	1/4 (25)	3/4 (75)	3/5 (60)	2/5 (40)	.52
Unresponsiveness	9	1/6 (16.7)	5/6 (83.3)	3/3 (100)	0/3 (0)	.05
Barotrauma	9	0/3 (0)	3/3 (100)	4/6 (66.7)	2/6 (33.3)	.17
$AaDo_2$ (≥610 × 8 h or ≥605 × 4 h [with PIP ≥38 cm H_2O])	9	4/8 (50)	4/8 (50)	0/1 (0)	1/1 (100)	1.00

*MMC indicates Maine Medical Center; ECMO, extracorporeal membrane oxygenation; CLD, chronic lung disease; $AaDo_2$, alveolar-arterial oxygen gradient; and PIP, peak inspiratory pressure.

†Two-tailed Fisher's exact test.

peak inspiratory pressure (PIP) of 38 or greater has been associated with an 80% or greater mortality in the literature.[5] The corresponding mortality for this criterion in each of the two medical centers is much lower (27.3% at MCHV, 46.7% at MMC). An oxygenation index (OI = mean airway pressure × fraction of inspired oxygen × 100/postductal arterial oxygen pressure [Pao_2]) greater than or equal to 40 has been reported to be associated with a 90% mortality incidence in patients with respiratory failure.[1] In contrast, an oxygenation index of 40 or greater at MCHV was associated with a 21.4% mortality. No data for an oxygenation index are available from MMC.

This and another study[14] iterate the importance of evaluating one's own population as to the need and indications for ECMO before committing enormous personnel and financial resources. Regionalization of ECMO programs would maximize care and expertise, as well as minimize duplication of services. With respect to the needs for Vermont and Maine, it would be prudent to participate in a regional ECMO program by referring potential ECMO patients to an established regional ECMO center.

Additional critical questions remain for the use of ECMO. First, is there a real need for ECMO? At this time, there probably is some need. It is reasonable to speculate that the "perceived" need can be minimized through improved conventional ventilatory management. Wung et al[26] and Dworetz et al[9] have each demonstrated improved outcome of critically ill neonates with persistent pulmonary hypertension with conservative, conventional ventilatory assistance and without ECMO.

Assuming that a small population of neonates exists that cannot be managed with conventional ventilation, how does one select the patient who would benefit from ECMO? Presently, there is no simple answer. Previously published experiences with ECMO have little or no scientific documentation to support the validity of mortality risks or specific respiratory selection criteria.[22,27-35] The meager data on which specific mortality risk assessments have been made were derived retrospectively on small sample sizes several years ago and not subjected to prospective evaluation. The neonatal pulmonary insufficiency index proved not to be predictive of mortality. Similarly, criteria based on various calculated alveolar-arterial oxygen gradients ($AaDo_2$) may yield false-positive and false-negative risk assessment due to manipulation of carbon dioxide (Pco_2) and oxygen pressures (PO_2) with hyperventilation.[11] Selection criteria based on the oxygenation index have been proposed[1,36] without prospective validation. High ventilatory rates, inadvertent positive end-expiratory pressure (PEEP), and measurement of mean airway pressure may alter the real vs the calculated oxygenation index.[37]

Our study and others suggest that it may be invalid to utilize one's own past and/or published criteria for predicting mortality risk and ECMO eligibility.[9,10] Ideally, ECMO patient selection criteria must identify the neonate in a given population who will suffer an adverse outcome of death or severe chronic lung disease with optimal conventional ventilatory therapy. The ECMO selection criteria should simultaneously exclude the critically ill, hypoxic neonate who will survive without ECMO and without severe chronic lung disease.[11]

It is no surprise that the applicability of ECMO patient selection criteria varies among institutions and even within the same institution over time. Mortality risks change over time. Therefore, the accuracy of selection criteria will be affected by many factors as follows: (1) the prevalence of adverse outcome in a population (eg, severe respiratory failure, chronic lung disease, and death); (2) the frequency and etiology of underlying disorders; and (3) the various managements of neonates with respiratory failure. It is possible that no criterion can be reliably applied over time even within the same institution. However, each institution and region should strive to develop and evaluate prospectively selection criteria.

Therefore, another new innovative and invasive, high-risk medical technology thrives among controversy as to its need and indications. Patient selection remains a real problem. Prevention of severe respiratory failure by minimizing the occurrence of severe asphyxia neonatorum, by maximizing resuscitation results, and by improving conventional ventilatory management should help to reduce the "need" for ECMO.

The authors wish to thank Jerold F. Lucey, MD, for advice and review of the manuscript; George E. Cole, Jr, MS, for computer programming; Joan McClallen, MS, for statistical analysis; and Deborah Cutler for manuscript preparation.

References

1. Ortiz RM, Cilley RE, Bartlett RH: Extracorporeal membrane oxygenation in pediatric respiratory failure. *Pediatr Clin North Am* 1987; 34:39-46.

2. Short BL, Miller MK, Anderson KD: Extracorporeal membrane oxygenation in the management of respiratory failure in the newborn. *Clin Perinatol* 1987;14:737-748.

3. Bartlett RH, Roloff DW, Cornell RG, et al: Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. *Pediatrics* 1985;76:479-487.

4. Bartlett RH, Toomasian J, Roloff D, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure—100 cases. *Ann*

Surg 1986;204:39-47.

5. Miller MK, Short BL, Glass P, et al: Outcome of 100 infants treated with extracorporeal membrane oxygenation (ECMO), abstracted. *Pediatr Res* 1987;21:369.

6. Bartlett RH: *ECMO Central Registry.* Ann Arbor, Mich, University of Michigan, February 1988.

7. Paneth N, Wallenstein S: Extracorporeal membrane oxygenation and play the winner rule. *Pediatrics* 1985;76:622-623.

8. Ware JH, Epstein MF: Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. *Pediatrics* 1985;76:849-850.

9. Dworetz AR, Fernanado RM, Sabo B, et al: Survival in infants with persistent pulmonary hypertension (PPHTN) without extracorporeal membrane oxygenation (ECMO), abstracted. *Pediatr Res* 1987;21:360.

10. Shelton CK, Gonzales F: Patient selection for extracorporeal membrane oxygenation (ECMO): Importance of individual institutional reviews, abstracted. *Pediatr Res* 1987;21:376.

11. Marsh TD, Wilderson SA, Cook LN: ECMO selection criteria: Pao$_2$ vs AaDo$_2$. *Pediatrics* 1988;82:162-166.

12. Schapira D, Solimano A: Is extracorporeal membrane oxygenation (ECMO) necessary to reduce mortality and morbidity in patients with meconium aspiration syndrome (MAS)? abstracted. *Pediatr Res* 1988;22:424.

13. Davis JM, Spitzer AR, Cox C, et al: Predicting survival in infants with persistent pulmonary hypertension of the newborn, in Lucey JF: *Two Great Debates in Neonatology, Ross Laboratories Special Conference.* 1987, p 114.

14. Southgate WM, Kanto WP: Defining the need for ECMO in Georgia, in *Two Great Debates in Neonatology, Ross Laboratories Special Conference,* 1987, pp 124-125.

15. Towne BH, Lott IT, Hicks DA, et al: Long-term follow-up of infants and children treated with extracorporeal membrane oxygenation (ECMO): A preliminary report. *J Pediatr Surg* 1985;20:410-414.

16. Sell LL, Cullen ML, Whittlesey GC, et al: Hemorrhagic complications during extracorporeal membrane oxygenation: Prevention and treatment. *J Pediatr Surg* 1986;21:1087-1091.

17. Schumacher RE, Barks JDE, Johnston MV, et al: Right-sided brain lesions in infants following unilateral carotid ligation for extracorporeal membrane oxygenation, abstracted. *Pediatr Res* 1987;21:375.

18. Ichord E, Kapur S, Short BL, et al: Neuropathologic findings in neonatal ECMO, abstracted. *Pediatr Res* 1988;22:411.

19. Glass P, Short BL: ECMO: Developmental outcome at age 2, abstracted. *Pediatr Res* 1988;22:447.

20. Reznik VM, Griswold WR, Telsey AL, et al: Systemic hypertension in infants after treatment with extracorporeal membrane oxygenation (ECMO), abstracted. *Pediatr Res* 1988;22:423.

21. Short BL, Anderson K, Arensman R, et al (ECMO Standards Committee): Guidelines for neonatal ECMO programs, in: *Two Great Debates in Neonatology, Ross Laboratories Special Conference.* 1987, pp 27-65.

22. Loe WA, Graves ED, Ochsner JL, et al: Extracorporeal membrane oxygenation for newborn respiratory failure. *J Pediatr Surg* 1985;20:684-688.

23. Trento A, Griffith BP, Hardesty RL: Extracorporeal membrane oxygenation experience at the University of Pittsburgh. *Ann Thorac Surg* 1986;42:56-59.

24. Weber TR, Pennington DG, Connors R, et al: Extracorporeal membrane oxygenation for newborn respiratory failure. *Ann Thorac Surg* 1986;42:529-535.

25. Redmond CR, Graves ED, Falterman KW, et al: Extracorporeal membrane oxygenation for respiratory and cardiac failure in infants and children. *J Thorac Cardiovasc Surg* 1987;93:199-204.

26. Wung JT, James LS, Kilchevsky E, et al: Management of infants with severe respiratory failure and persistence of fetal circulation, without hyperventilation. *Pediatrics* 1985;76:488-494.

27. Bartlett RH, Gazzaniga AB, Fong SW, et al: Extracorporeal membrane oxygenator support for cardiopulmonary failure: Experience in 28 cases. *J Thorac Cardiovasc Surg* 1977;73:375-386.

28. Bartlett RH, Gazzaniga AB, Huxtable RF, et al: Extracorporeal circulation (ECMO) in neonatal respiratory failure. *J Thorac Cardiovasc Surg* 1977;74:826-833.

29. Wetmore N, McEwen D, O'Connor M, et al: Defining indications for artificial organ support in respiratory failure. *Trans Am Soc Artif Intern Organs* 1979;25:459-461.

30. Hardesty RL, Griffith BP, Debski RF, et al: Extracorporeal membrane oxygenation: Successful treatment of persistent fetal circulation following repair of congenital diaphragmatic hernia. *J Thorac Cardiovasc Surg* 1981;81:556-563.

31. Bartlett RH, Andrews AF, Toomasian JM, et al: Extracorporeal membrane oxygenation for newborn respiratory failure: Forty-five cases. *Surgery* 1982;92:425-433.

32. Krummel TM, Greenfield LJ, Kirkpatrick BV, et al: Clinical use of an extracorporeal membrane oxygenator in neonatal pulmonary failure. *J Pediatr Surg* 1982;17:525-531.

33. Kirkpatrick BV, Krummel TM, Mueller DG, et al: Use of extracorporeal membrane oxygenation for respiratory failure in term infants. *Pediatrics* 1983;72:872-876.

34. Krummel TM, Greenfield LJ, Kirkpatrick BV, et al: Alveolar-arterial oxygen gradients vs the neonatal pulmonary insufficiency index for prediction of mortality in ECMO candidates. *J Pediatr Surg* 1984;19:380-384.

35. Beck R, Anderson KD, Pearson GD, et al: Criteria for extracorporeal membrane oxygenation in a population of infants with persistent pulmonary hypertension of the newborn. *J Pediatr Surg* 1986;21:297-302.

36. Ortega M, Ramos A, Atkinson J, et al: Oxygenation index can predict outcome in neonates who are candidates for extracorporeal membrane oxygenation, abstracted. *Pediatr Res* 1987;21:462.

37. Purohit DM, Patrick CH: ECMO: Comments on selection criteria, in: *Two Great Debates in Neonatology, Ross Laboratories Special Conference.* 1987, pp 126-128.

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Glutaric Acidemia Type II: Comparison of Pathologic Features in Two Infants

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Reflex Sympathetic Dystrophy Syndrome in Children and Adolescents

Report of 18 Cases and Review of the Literature

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• Reflex sympathetic dystrophy syndrome is a well-recognized disorder in adults, but it is rarely diagnosed in the pediatric age group. This report summarizes our experience with this condition from 1975 to 1985. We diagnosed, treated, and followed up this condition in 18 children and adolescents. The condition usually followed trauma. The most prominent feature in all patients was a constant limb pain with episodes of paroxysmal exacerbation. The pain was associated with two or more of the following: edema, hyperhidrosis or anhidrosis, cyanosis or erythema, and, in severe cases, dystrophic skin changes and muscle atrophy. Roentgenograms were normal. Bone scans were helpful to exclude other possible causes of bone and joint pain. Reflex sympathetic dystrophy syndrome in children probably often goes unrecognized, sometimes being confused with psychiatric conditions such as conversion reaction and malingering. Reflex sympathetic dystrophy syndrome should always be considered in the differential diagnosis of unexplained persistent limb pain in children: early recognition and proper management may result in the prevention of potentially crippling sequelae.

(*AJDC* 1988;142:1325-1330)

Reflex sympathetic dystrophy syndrome (RSDS) is a well-recognized entity associated with a variety of precipitating factors, most commonly with a history of minor trauma. The classic signs, painful swelling in an extremity, fluctuating vasomotor changes, and dystrophic skin and muscle changes, have been given different names such as causalgia,[1] Sudeck's atrophy,[2] and shoulder-hand syndrome.[3] Other synonyms include the following: algoneurodystrophy,[4] angiospastic syndrome,[5] hyperesthesic neurovascular syndrome,[6] minor causalgia,[6] neuroalgodystrophy,[7] posttraumatic osteoporosis,[8] posttraumatic sympathetic dystrophy,[9] reflex neurovascular dystrophy,[10] and vasospastic disorder.[11] The proliferation of terminology that evolved over time[1-11] addresses the multifaceted presentation. Although generally considered an "adult disease," cases of RSDS have been occasionally described in the pediatric literature.[9,10,12-22] We had the opportunity to observe and follow up 18 patients afflicted with RSDS. The course of this illness will be presented with emphasis on two patient reports illustrating the severe and moderate forms. Current concepts about the clinical spectrum, etiology, and management of RSDS will be discussed.

RSDS: PATIENT REPORTS

The diagnosis of RSDS was made on a clinical basis whenever a patient with a painful limb presented two or more of the following signs and symptoms: persistent pain and swelling (hyperpathia, hyperesthesia), vasomotor instability (vasoconstriction, vasodilatation), trophic skin changes in the same extremity (skin atrophy, pigmentary changes, hyperhidrosis, muscle atrophy), and autonomic imbalance.[23] Eighteen children and adolescents had their conditions diagnosed by us between 1975 and 1985 (Table 1). The age range was 9 to 19 years with a median of 14 years. The sex distribution showed moderate female predominance: seven boys and 11 girls. It was more common in a lower limb (n = 11) than in an upper limb (n = 7). There was a history of trauma (mild to moderate) in almost all patients and the duration of illness ranged from one to six months.

Pain was the most prominent feature of RSDS in our 18 patients. It was described by our patients as a burning sensation, aching and sharp, but occasionally it was depicted as dull or throbbing. The pain was usually continuous with episodes of paroxysmal worsening. Often the pain was provoked by manipulation, or it was associated with stress. The pain was initially localized to the foot or hand and progressed, in one fourth of the patients, to about half of the affected limb. The pain was not limited to a dermatome. Hyperesthesia was present in all our patients. Marked vasomotor disturbances afflicted three fourths of our patients. It manifested variously as vasoconstriction (cyanosis, cold extremity) or vasodilatation (warm, erythematous skin). The severity of these symptoms varied from one patient to the other, sometimes even for the same patient at different times. Most patients had persistent edema of the affected extremity. The trophic changes, so commonly described in adults with RSDS, were only seen in the most severe cases and were completely reversible. There was no bone atrophy among our patients.

Psychologic characteristics that were observed singly or in combination in our patients included dependent personality traits, avoidance of responsibility, low pain threshold, chronic complaining, insecurity, anxiety, and depression. While some patients demonstrated an inclination to "milk" their disability by apparently exaggerating the severity of their symptoms, others seemed to have a lack of concern about their injury and would use rationali-

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Accepted for publication Aug 2, 1988.

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Read before the 18th International Congress of Pediatrics, Honolulu, July 11, 1986.

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Table 1.—Reflex Sympathetic Dystrophy Syndrome (n = 18)*

Age, y/ Sex/Limb	History of Trauma	Pain/ Hyperesthesia	Swelling/ Vasomotor Instability	Bone Scan	Degree of Illness	Treatment
15/M/L	+	+	+	+	Mod	PT
15/F/L	−	+	+	+	Sev	PT-GB
16/M/L	+	±	−	ND	Mod	PT
15/M/L	+	±	−	ND	Mod	PT
17/F/U	+	+	+	ND	Mod	PT
19/M/U	+	±	±	ND	Mod	PT
14/F/U	−	+	+	+	Sev	PT-GB
16/F/U	−	+	+	+	Sev	PT
11/M/U	+	+	+	+	Sev	PT-GB
12/M/L	+	+	+	+	Mod	PT
16/F/L	+	+	+	+	Sev	PT-GB
13/F/L	+	+	+	+	Sev	PT
9/F/L	+	+	+	+	Sev	PT-GB
10/M/L	+	+	±	+	Mod	PT
12/F/L	+	±	±	+	Mod	PT
10/F/L	+	+	±	+	Sev	PT
16/F/U	+	+	±	+	Mod	PT
15/F/U	+	+	±	ND	Mod	PT

*U indicates upper; L, lower; ND, not done; Mod, moderate; Sev, severe; PT, physiotherapy; GB, ganglion block; plus sign, present; minus sign, absent; and plus/minus sign, sometimes present.

Table 2.—Gradations of Reflex Sympathetic Dystrophy Syndrome*

	Grade 1 (Severe)	Grade 2 (Moderate)	Grade 3 (Mild)
Pain	Stabbing, lancinating, burning, not relieved by rest, aggravated by emotional and physical disturbances	Dull, aching, diffuse, mostly aggravated by motion, often relieved by rest	Insidious onset, reluctance to active and passive motion
Vasomotor	Severe vasoconstriction (ice-cold skin, thin, cyanotic, glistening, profuse perspiration), severe vasodilatation (hot, red, dry, scaly skin)	Moderate vasomotor changes: skin can be cold and clammy or hot and dry	Mild changes, but temperature and color are different from the other extremity
Trophic	Fixed, voluntary immobility and firm resistance to motion over time may result in trophic changes of skin and subcutaneous tissue (and eventually of muscles and bones)	The milder course may result in diagnostic delay and consequently osteoporosis may be a finding when initially seen	Usually absent, but may have local edema

*According to Betcher and Casten.[24]

zations for not following the physician's recommendations. Before obtaining bone scans, physicians reported that six of 18 patients were "hypersensitive" or suffering from "functional pain." Characteristically, our patients were "sympathetic hyperreactors" as evidenced by a personal history of poor cold tolerance and increased sweating of palms and soles. More importantly, many were clearly emotionally labile.

Diagnostic procedures were not necessary to make the diagnosis but were considered useful in ruling out other possible causes of pain. Roentgenograms were normal in all patients except for mild osteoporosis in the limb of one patient. The bone scan, however, was abnormal in all 13 patients in whom it was performed. We classified our patients into three grades following the categories of Betcher and Casten[24]: severe (grade 1), moderate (grade 2), and mild (grade 3) (Table 2). Eight of our patients suffered grade 1 disease and the rest were classified as having grade 2. We suspected grade 3 in an additional 21 patients but decided to exclude them from our series because it is actually difficult to prove that they had RSDS: they recovered within a month.

The following two case histories illustrate the classic characteristics of the severe and moderate form of this disorder.

RSDS Grade 1 (Severe)

A 14-year-old left-handed female adolescent was treated for malnutrition secondary to anorexia nervosa and depression. She was seen because of pain and swelling of her left dominant hand. She complained about flashes of pain and changes of color, ranging from bright red to pale, and "fever" in her hand. She could not remember any trauma, although she recalled slipping during a hockey game. Her stepmother remembered that during a meal the patient had a temper tantrum and violently threw her food away banging the table with her left hand.

The patient was brought to the attention of the physical medicine consultant who, after ruling out a carpal tunnel syndrome, agreed with the diagnosis of RSDS. The patient did not follow through with the recommended physiotherapy, held her limb in a dependent position, and refused to use it. She behaved as if her hand did not belong to her. Her psychotherapist became concerned with her lack of collaboration and interpreted that the child was actually "punishing the hand that fed her." Her hand became colder, cyanotic, edematous, and somewhat atrophic (Fig 1). A bone scan showed decreased blood flow and markedly decreased tracer uptake in the bones of the left hand (Fig 2).

She was hospitalized. Initially she did not respond to nutritional rehabilitation, around-the-clock physical therapy, transcutaneous nerve stimulation, and systemic corticosteroid therapy. She also received intensive psychotherapy and psychopharmacotherapy (initially tricyclic antidepressants, later on lithium carbonate). Gradually her malnutrition was corrected and her mood improved, yet her RSDS remained unchanged. She was then given a series of eight sympathetic blocks, which produced Horner's syndrome, and favorable plethysmographic changes in her fingers, followed finally by a dramatic clinical improvement. She recovered the color and mobility of her limb and started to use it again. In total she spent three months in the hospital. At six months follow-up, her depression and anorexia nervosa had lifted and her RSDS was cured.

RSDS Grade 2 (Moderate)

A 15-year-old male adolescent was seen in consultation because of a painful left leg.

He gave a history of minor trauma to the leg in the preceding three months and a fracture in the same leg a year earlier. No abnormality was detected and he was reassured. One week later, however, the pain had localized in his left foot. He reported that the pain was severe, and that at times the foot was "hot and red."

The patient was hospitalized for observation. Various subspecialists were consulted and the following other conditions were considered and discarded: thrombophlebitis, Baker's cyst, compartment syndrome, and early osteomyelitis. Results of his extensive evaluation were normal except for a bone scan that showed decreased uptake in the left foot consistent with RSDS. In the hospital he developed a severe limp and resorted to using crutches. He was treated with analgesics and steroids and received intensive physiotherapy. After three weeks he was persuaded to use his extremity. The course of his illness was of three months' duration. During this time moderately serious neurotic problems dealing with issues of self-esteem and depression were uncovered and he agreed to become involved in psychotherapy. There was one mild relapse several months later that responded promptly to physical therapy; he recovered completely.

The course of the disease in our 18 patients was variable but it tended to follow the three stages of illness reported by Bonica[25] (Table 3). The first stage was announced by pain, hyperesthesia, and localized edema. This led to limitation of motion. The skin, which started out being warm, red, and dry, then became cold, moist, and cyanotic. The second stage followed after one or more months of illness. Pain decreased, edema spread, the joint thickened, and there was muscle wasting. Only one patient entered the early third stage, when the affected limb turned cold, pale, or cyanotic, with smooth glossy atrophic skin, brittle nails, diminished subcutaneous tissue, weakness, and muscle wasting. With appropriate management all our patients recovered; none developed bone atrophy. The treatment of choice for most of our patients was physical therapy. The patients with more severe conditions required steroid therapy and ganglion blocking. Our long-term follow-up (ranging from one to ten years) showed all patients functioning normally. However, one patient experienced a mild episode of pain and intermittent swelling and another had a frank recurrence.

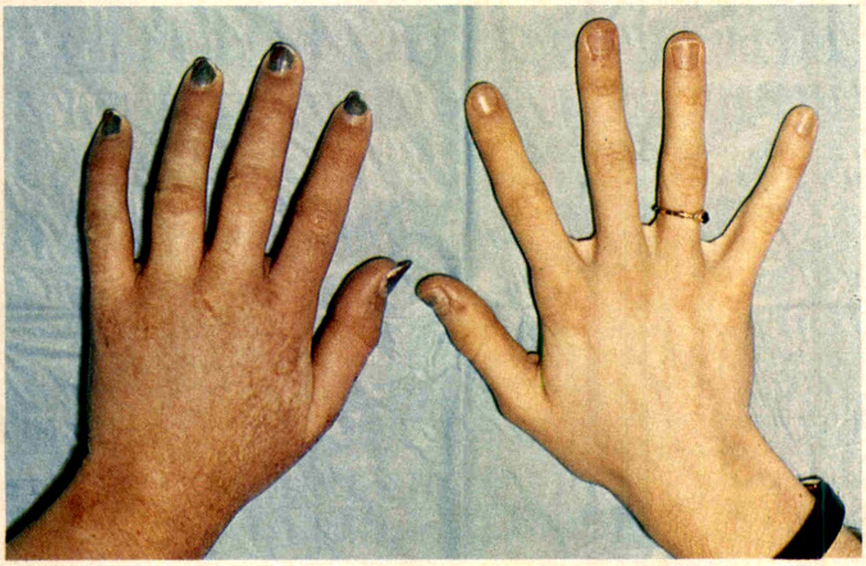


Fig 1.—Reflex sympathetic dystrophy syndrome. Note edema and cyanosis of left hand.

COMMENT

The history of this complex condition goes back to the 19th century, when RSDS was first identified in the United States in soldiers wounded during the Civil War.[1] At the beginning of this century, Sudeck,[2] in Germany, correlated the symptoms with radiologic changes. In 1926, Leriche and Policard,[26] in France, were the first to suggest that the neurovegetative system was involved in the pathogenesis of RSDS. Since then, the syndrome has been recognized frequently

Fig 2.—Bone scan of hands. Left, Early image obtained shortly after injection of technetium Tc 99m methylene diphosphonate shows decreased blood flow to left hand. Right, Delayed image obtained three hours later shows retention of tracer in edematous soft tissues of left hand with markedly decreased uptake in bones.

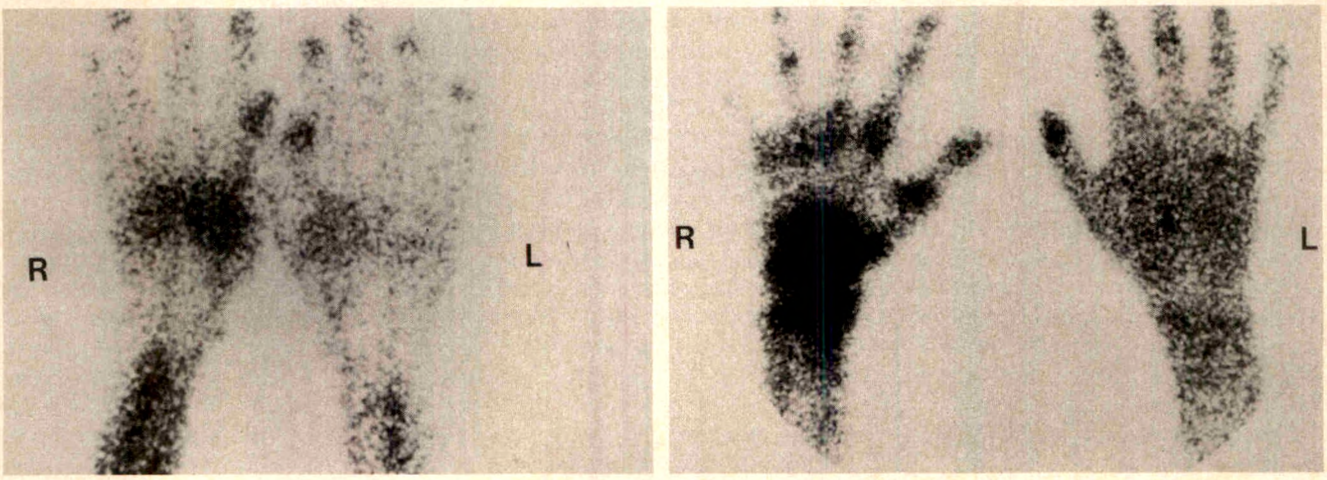


Table 3.—Course of the Reflex Sympathetic Dystrophy Syndrome (RSDS)*

Acute Stage: Intense pain, hyperesthesia, and edema associated with vasodilatation and vasoconstriction lead to immobility. There is development of a "causalgic personality": all priority goes to protecting the limb from pain.

Established RSDS (Dystrophic Stage): After a month or more, pain diminishes but the edema spreads. The joints begin to thicken and muscle wasting becomes noticeable. The limb is not being used.

Sequelae (Atrophic Stage): There may or may not be pain but the limb is cold, cyanotic, with diminished subcutaneous tissue, weak, wasted muscles, smooth glossy atrophic skin, and brittle nails. At the end there is complete loss of limb function and bone atrophy (osteoporosis).

*Mild forms of RSDS may resolve spontaneously. The more severe forms may not leave sequelae if properly treated.

in the adult, and while clearly associated with trauma in most instances, it has also been described in association with myocardial infarction, abnormality of the cervical spine, and a variety of central nervous system lesions.[28] In children and adolescents, however, most cases seem to be related to trauma and stress.[9,10,13,17] The condition may have its onset days, weeks, or months after the initial event.

The diagnosis is based on clinical characteristics.[10,13,21,23] Some of our patients had been reported to be "hysterical," "hypochondriac," or "malingerers." While these diagnoses were incorrect, they point to the need for establishing a differential diagnosis between RSDS and conversion disorder and factitious illness.

The roentgenographic studies are usually normal. In adults the bone scan may show increased blood flow and increased periarticular uptake of the tracer.[27] In children, however, this scintigraphic pattern is seen in only about 20% of the cases. A more common pattern is that of decreased blood flow to the affected extremity and decreased osseous uptake of the tracer.[16,20] A normal scan does not exclude the diagnosis. Another noninvasive technique, thermography, has also been used recently to document the diagnosis by reproducing graphically the diffuse thermal alterations seen in RSDS.[22]

The etiology of RSDS is a subject of intense speculation. An early theory proposed that since symptoms may develop after soft-tissue trauma as well as after nerve injury, it is conceivable that minuscule peripheral nerve twigs could be damaged and form artificial synapses, resulting in ephaptic transmission between sensory afferents and sympathetic efferents. In turn, this event would increase input into the spinal cord and intensify the activity of the internuncial neuron pool, thus establishing a vicious circle of pain and sympathetic hyperactivity.[28] An alternative explanation, developed later, involved the brain-stem reticular formation acting as a "central biasing mechanism" exercising inhibitory influence on transmission at synaptic levels.[29] Accordingly, whenever a loss of sensory fibers occurs, this may result in a decrease of input from the affected limb and, consequently, in a decreased influence of the biasing mechanisms. In addition, prolonged pain may leave "memory traces" in the somatesthetic system, making an individual more susceptible to recurrent pain.[29]

More recently, another group of authors considered that the manifestations of RSDS are the expression of local sympathetic nervous system overactivity.[30] In support of this view, they cited studies utilizing oscillography, plethysmography, skin temperature measurements, and venous blood gas determinations demonstrating increased blood flow and increased venous oxygen saturation in affected extremities. They also pointed out that synovial biopsy specimens in patients with RSDS show a unique histologic appearance, characterized by proliferation and disarray of synovial lining cells and by increased numbers of small blood vessels. Similar changes have been induced in animals after limb immobilization and by direct irritation of the stellate ganglion.[30] Current physiologic research suggests that RSDS may arise from injury or inflammation damage to Schwann's cells followed by the development of abnormal electrogenic properties in regions of demyelinization and sprout outgrowth. A demyelinated segment may acquire ectopic pacemaker capability and chemosensitivity. It is therefore probable that the hyperalgesia of RSDS may be due to similar membrane changes in cutaneous axon terminals.[31] Thus, based on present scientific evidence, it may be concluded that RSDS is the result of abnormal firing by damaged peripheral nerves.[32] However, there is also a clear role for cortical centers in modulating the pain and vasomotor activity.[33]

Many clinicians have described a high index of neuroticism in patients afflicted by RSDS.[7,10,14] We agree and consider that a susceptible population exists. Moreover, we observed an interrelationship between a history of physiologic symptoms of sympathetic hyperreactivity and psychologic stress at the onset of RSDS. A psychophysiologic explanation is also compatible with the observation that many patients tend either to exaggerate or to minimize the significance of their injury. Whether there is conscious or subconscious input following the initial causal event or whether the peripheral abnormality is exclusively responsible for RSDS and the emotional distress is only reactive is still open to debate. Yet, regardless of the initial event, the subsequent concomitant existence of physiologic and psychologic symptoms has been well documented.[10] Thus, whether or not psychologic factors predispose to the development of RSDS, they certainly can aggravate it. Reflex sympathetic dystrophy syndrome in the young has a clear sex predilection: it is more prevalent among adolescent girls despite the fact that soft-tissue trauma is more common in boys. Perhaps this may reflect another manifestation of the increased tendency (when compared with males) toward stress-related and psychosomatic illnesses in young women.[10]

We acknowledge, however, that another possible interpretation for the psychopathologic conditions we noted in our patients with RSDS exists, namely, that it be explained by the duration of their pain. The classic medical literature on pain shows that its expression is determined by a multiplicity of cultural and psychologic factors.[34] Studies of patients with pain reveal that those presenting with acute pain tend to have normal personality profiles, but that the degree of pain experienced is related to the degree of anxiety present.[35] Finally, it has been shown that when pain becomes chronic, most patients show somatic preoccupations and reactive depression,[36] and patients with RSDS may be no exception to this rule.

Etiologic and physiopathologic speculations have given rise to a large and varied number of treatment strategies ranging from more conservative measures (eg, physiotherapy,[37] temperature biofeedback,[38] behavioral therapy,[39] and transcutaneous nerve stimulation[40]) to pharmacotherapy (eg, oral corticosteroids,[41] calcitonin,[42] nifedipine,[43] phenoxybenzamine hydrochloride,[44] or prazosin hydrochloride[11]) to more aggressive measures (eg, stellate ganglion blocking,[45] intravenous regional guanethidine and reserpine,[46] prolonged procaine amide infusion into the stellate ganglion,[47] and even surgery [sympathectomy][48]). With such an abundance of theories and treatments, the pediatrician has an important role in coordinating care and consultations. In our experience, the most important factor in the effective treatment of RSDS was early recognition and not allowing the patient to adopt the "sick" role. Avoidance of immobilization at all costs and early physical therapy led to recovery in patients with milder cases and were important ingredients in the management of the more severe forms. We have been favorably impressed by the effectiveness of sympathetic blocks when other treatment modalities failed, and so far we have never needed to perform a ganglionectomy.

In every instance of RSDS the patient should be counseled, encouraging limb mobility and return to independence. Often additional problems are uncovered and psychotherapy will be clearly indicated. In patients with recalcitrant or recurrent RSDS, hospitalization for intensive treatment may be essential to good outcome.[10] Early recognition and early intervention remain the keys to successful treatment.

CONCLUSION

Children and adolescents with limb pain and swelling with hyperesthesia, vasomotor changes, or both are likely to suffer from RSDS. This condition has a wide clinical spectrum ranging from moderate complaints of pain and spontaneous resolution within one month to intractable pain and limb atrophy. Minor trauma and stress are believed to be triggering factors in predisposed children and adolescents, and sympathetic hyperactivity is suspected to be a predisposing factor. Reflex sympathetic dystrophy syndrome is triggered by abnormal firing from damaged peripheral nerves, causing altered response from neuronal pools in the spinal cord, which in turn respond to cortical influences. Psychologic factors may play an important role through either a cortical or subcortical input. Diagnostic ability may be enhanced by the use of bone scanning and thermography. The course of the disease is variable. Reflex sympathetic dystrophy syndrome may result in a life-style of invalidism, prolonged absence from school, and, on occasion, it may actually cripple physically and emotionally. The psychologic influence of persistent pain and the pathogenic contribution of stress should always be considered. Initial therapy includes prompt intensive physiotherapy and behavioral management. Psychotherapy is clearly indicated in patients with dysfunctional behavior who may become entrenched in the "sick" role. Patients with severe conditions may require hospitalization, corticosteroid therapy, sympathetic ganglion blocking, and even surgery (sympathectomy). The pediatrician may fulfill an essential role providing early diagnosis, coordination of the treatment program, and counseling throughout the course of RSDS.

Helga Binder, MD (Physical Medicine); Michael Abramowitz, MD, and George Morales, MD (Anesthesiology); Patience White, MD (Rheumatology); Arnold Gale, MD (Neurology); Calvin Sumner, MD (Psychiatry); and Dennis Johnson, MD, and Kathryn Hammock, MD (Neurosurgery) provided valuable consultation in patient care and contributed to our understanding of RSDS. Irene Chatoor, MD, Peter Goyer, MD, and Lawrence D'Angelo, MD, critically reviewed this manuscript.

References

1. Mitchell SW, Morehouse GR, Keen WW: *Gunshot Wounds and Other Injuries of Nerves.* Philadelphia, JB Lippincot, 1864.

2. Sudeck P: Über die akute entzundliche Knochenatrophie. *Arch Klin Chir* 1900;62:147-156.

3. Steinbroker O: The shoulder-hand syndrome. *Am J Med* 1947;3:402-407.

4. Glick EN: Reflex dystrophy (algoneurodystrophy): Results of treatment by corticosteroids. *Rheumatol Rehabil* 1973;12:84-88.

5. Morton JJ, Scott WJM: Some angiospastic syndromes in the extremities. *Am Surg* 1931; 94:839-842.

6. Homans J: Minor causalgia: A hyperesthesic neurovascular syndrome. *N Engl J Med* 1940;222:870-873.

7. Van Houdenhove B: Neuro-algodystrophy: A psychiatrist's view. *Clin Rheumatol* 1986; 5:399-406.

8. Fontaine R, Herrmann L: Posttraumatic osteoporosis. *Ann Surg* 1933;17:26-28.

9. Guntheroth WG, Chakmakjian S, Brena SC, et al: Posttraumatic sympathetic dystrophy. *AJDC* 1971;121:511-514.

10. Sherry DD, Weisman R: Psychologic aspects of childhood reflex neurovascular dystrophy. *Pediatrics* 1988;81:572-578.

11. Spittell JA: Vasospastic disorders. *Cardiovasc Clin* 1983;13:75-88.

12. Kozin F, Haughton V, Ryan L: The reflex sympathetic dystrophy in a child. *J Pediatr* 1977;90:417-419.

13. Fermaglich DR: Reflex sympathetic dystrophy in children. *Pediatrics* 1977;60:881-883.

14. Bernstein BH, Singsen BH, Kent JT, et al: Reflex neurovascular dystrophy in childhood. *J Pediatr* 1978;93:211-215.

15. Wettrell G, Hallbook T, Hultquist C: Reflex sympathetic dystrophy in two young females. *Acta Paediatr Scand* 1979;68:923-924.

16. Majd M: Bone scintigraphy in children with obscure skeletal pain. *Ann Radiol* 1979;22:85-88.

17. Ruggeri SB, Athreya BH, Doughty R, et al: Reflex sympathetic dystrophy in children. *Clin Orthop* 1982;163:225-230.

18. Buchta RM: Reflex sympathetic dystrophy in a 14-year-old female. *J Adolesc Health Care* 1983;4:121-122.

19. Rush PJ, Wilmot D, Saunders N, et al: Severe reflex neurovascular dystrophy in childhood. *Arthritis Rheum* 1985;28:952-956.

20. Laxer RM, Allen RC, Malleson PN, et al: Technetium 99 m methylene disphosphonate bone scans in children with reflex neurovascular dystrophy. *J Pediatr* 1985;106:437-440.

21. Forster RS, Fu FH: Reflex sympathetic dystrophy in children. *Orthopedics* 1985;8:475-477.

22. Lightman H, Pochaczevsky R, Hormozan A, et al: Thermography in childhood reflex sympathetic dystrophy. *J Pediatr* 1987;111:551-555.

23. Kozin F, McCarty DJ, Sims J, et al: The reflex sympathetic dystrophy syndrome: Clinical and histologic studies: Incidence for bilaterality, response to corticosteroids and articular involvement. *Am J Med* 1976;60:321-331.

24. Betcher AM, Casten DR: Reflex sympathetic dystrophy: Criteria for diagnosis and treatment. *Anesthesiology* 1955;16:994-1003.

25. Bonica JJ: Causalgia and other reflex sympathetic dystrophies. *Postgrad Med* 1973;53:143-148.

26. Leriche R, Policard J: *Les Problems de la Physiologie Normal et Pathologie de l'os.* Paris, Mason, 1926.

27. Kozin F, Soin JS, Ryan LM, et al: Bone scintigraphy in the reflex sympathetic dystrophy syndrome. *Radiology* 1981;138:437-443.

28. Drucker WR, Hubay CA, Holden WD, et al: Pathogenesis of posttraumatic sympathetic dystrophy. *Am J Surg* 1959;97:454-465.

29. Melzack R, Wall PD: Pain mechanisms: A new theory. *Science* 1965;150:971-979.

30. Kozin F, Genant H, Berkerman C: The reflex sympathetic dystrophy syndrome: Roentgenographic and scintigraphic evidence of bilaterality of a periarticular involvement. *Am J Med* 1976;60:332-338.

31. Devore M: Nerve pathophysiology and mechanisms of pain in causalgia. *J Auton Nerv Syst* 1983;7:371-384.

32. Schwartzman RJ, McLellan TL: Reflex sympathetic dystrophy: A review. *Arch Neurol* 1987;44:555-561.

33. Janig W: Central organization of somatosympathetic reflexes in vasoconstrictor neurons. *Brain Res* 1975;87:305-312.

34. Sternbach RA: *Pain Patients.* Orlando, Fla, Academic Press Inc, 1974.

35. Bonica JJ: Bonica JJ, Liebeskind JC, Albe Fessard DG (eds): *Advances in Pain Research and Therapy.* New York, Raven Press, 1979, vol 3, pp 141-166.

36. Sternbach RA: Psychophysiology of pain. *Int J Psychiatry Med* 1975;6:63-73.

37. Schutzer SF, Gossling HR: The treatment of the reflex sympathetic syndrome. *J Bone Joint Surg* 1984;66:625-629.

38. Barowsky EI, Zweig JB, Moskowitz J: Thermal biofeedback in the treatment of symptoms associated with reflex sympathetic dystrophy. *J Child Neurol* 1987;2:229-232.

39. Alioto JT: Behavioral treatment of reflex sympathetic dystrophy. *Psychosomatics* 1981;22:539-540.

40. Richlin DM, Carron H, Rowlingson JC, et al: Reflex sympathetic dystrophy: Successful treatment by transcutaneous nerve stimulation. *J Pediatr* 1978;93:84-86.

41. Kozin F, Ryan LM, Carrera GF, et al: The reflex sympathetic dystrophy syndrome: III. Scintigraphic studies, further evidence for the therapeutic efficacy of systemic corticosteroids. *Am J Med* 1981;70:23-30.

42. Williame E: Le traitement de l'algodystrophie sympatique par la calcitonine. *Rev Med Brux* 1980;1:457-462.

43. Prough DS, McLeskey CH, Poehling GG, et al: Efficacy of oral nifedipine in the treatment of reflex sympathetic dystrophy. *Anesthesiology* 1985;62:796-799.

44. Ghostine SY, Commair YG, Turner DM, et al: Phenoxybenzamine in the treatment of causalgia. *J Neurosurg* 1984;60:1263-1268.

45. Wang JK, Johnson KA, Ilstrup DM: Sympathetic blocks for reflex sympathetic dystrophy. *Pain* 1985;23:13-17.

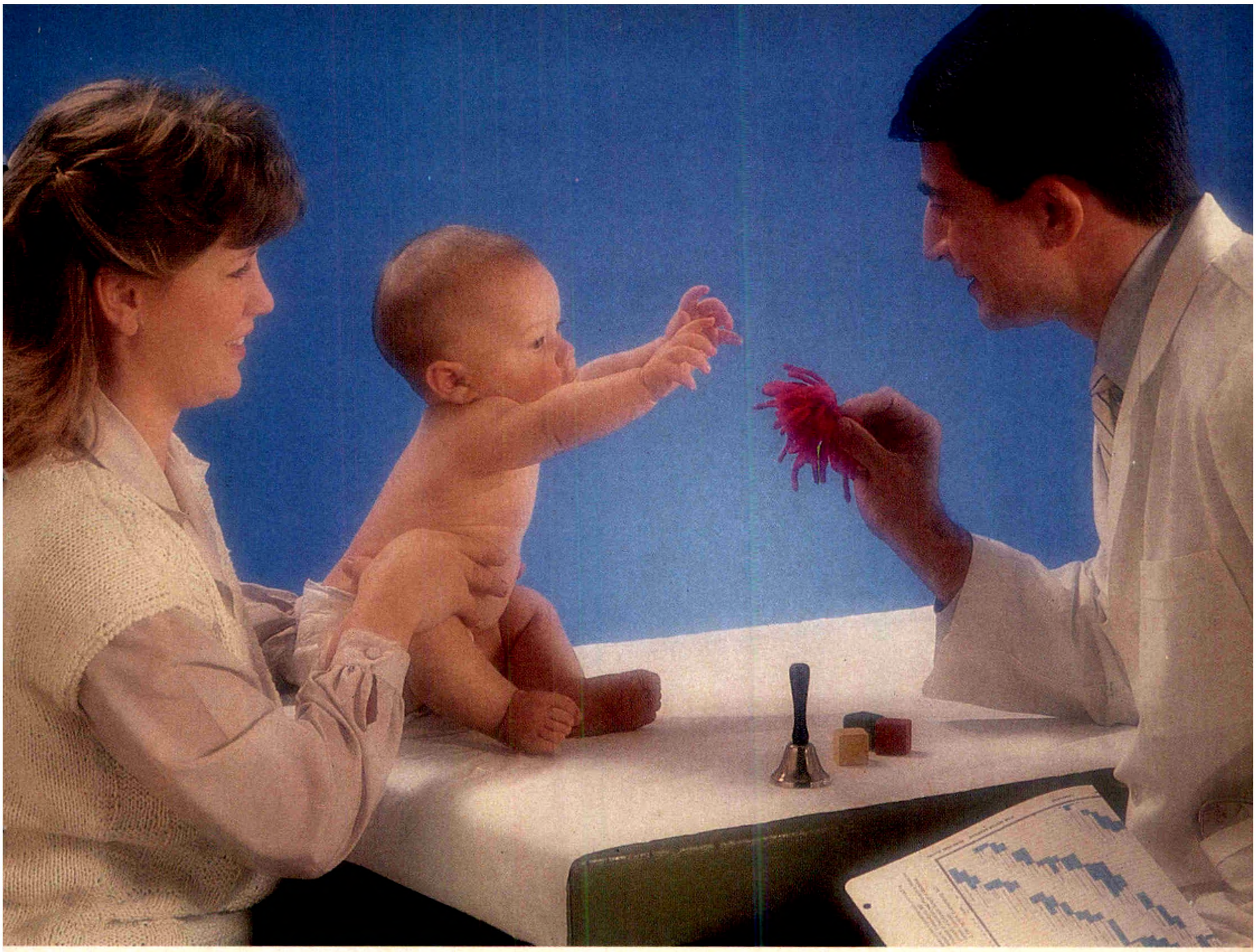
46. McKain CV, Urbon BJ, Goldner JL, et al: The effects of intravenous regional guanethidine and reserpine. *J Bone Joint Surg* 1983;65:808-811.

47. Leipzig TJ, Mullen SF: Causalgic pain relieved by prolonged procaine amide sympathetic blockage. *J Neurosurg* 1984;60:1095-1096.

48. Erdemir H, Gelman D, Gailbraith JG: Prediction of the needed level of sympathectomy for posttraumatic reflex sympathetic dystrophy. *Surg Neurol* 1987;17:353-354.

CORRECTION

Incorrect Phrasing.—In the article entitled "Familial Glucocorticoid Deficiency in a Girl With Hypophosphatemic Rickets," published in the August 1988 issue of *AJDC* (1988;142:900-903), errors occurred in the text. On page 901, at the end of the third sentence, the parenthetical statement "(all values 2.8 µmol/d)" should have read "(all values <2.8 µmol/d)." In the "Comment" section, the fourth sentence should have read as follows: "Patients with FGD often have tall stature,[6-8] and it has been speculated that their relative lack of cortisol may play a role because the effects of growth hormone and other anabolic compounds are unopposed.[6]"



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References:

1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986, pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharmacy Times* 1985;51(1):80-90.

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Pediatric Perspectives

Surfactant Replacement

A New Era With Many Challenges for Neonatal Medicine

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Exogenous surfactant therapy offers great promise for reducing the severity, morbidity, and early mortality attributable to the respiratory distress syndrome (RDS). The RDS remains the primary cause of neonatal mortality; it is responsible for approximately one neonatal death per 1000 live births in the United States,[1] and it contributes to the number of infants with chronic pulmonary sequelae and neurodevelopmental handicaps, emphasizing the need to make efficacious therapies available throughout the world. Since 1959, surfactant deficiency has been recognized as primary in the pathogenesis of RDS[2]; RDS results in progressive atelectasis, ventilatory failure, and combined metabolic and respiratory acidosis, resulting in a "shocklike" state with multiorgan failure. However, RDS, a developmental disorder, is further complicated by neonatal maladaptation to extrauterine life and multiorgan immaturity, including prolonged patency of the ductus arteriosus, poorly regulated cerebral blood flow, gastrointestinal immaturity, limited renal function, and vulnerability to infection. The clinical use of exogenous surfactant replacement using aerosolized "pure" dipalmitoylphosphatidylcholine prior to 1970 was found to have little or no beneficial effect in RDS.[3] Chu and coworkers[4] found no effect of administered "surfactant," suggesting that other factors contributed to the development of RDS, including pulmonary hypoperfusion.

These early treatment failures prompted others to evaluate natural or "complete" surfactant, obtained by lung lavage. Enhorning and Robertson[5] first demonstrated an improvement in pulmonary mechanics and roentgenographic indexes and a decrease in atelectasis and lung pathology using a natural and complete surfactant in fetal rabbits. Adams and coworkers,[6] in fetal lambs, first established that exogenous surfactant supplementation could reverse neonatal respiratory failure in animal models of RDS. Their findings laid the foundation for the initiation of contemporary human clinical trials first reported by Fujiwara et al.[7] They also set the stage for the development of a variety of surfactants (natural homologous [ie, human, nonlipid extract], nonmodified or modified heterologous [ie, lipid extracts of lung washings or whole lung with or without supplementation of selected surfactant components], and synthetic (compounded from synthetic sources of phospholipids and emulsifiers]) presently being evaluated in clinical trials throughout the world.

PHARMACOLOGIC PROPERTIES OF SURFACTANT

Critical questions regarding which surfactant(s) should be added to the neonatologist's pharmacopeia require comprehensive study and satisfactory demonstration of both the short-term and long-term efficacy and safety for reversing respiratory failure caused by RDS. Furthermore, it must be demonstrated that this new treatment is not associated with the increased incidence of morbidity or neurodevelopmental handicap often encountered in tiny preterm infants. Shapiro[8] described the following desirable characteristics of exogenous surfactants considered for widespread use: efficacy in vitro (ie, biophysical activity of the surfactant as measured by the surface balance apparatus or a pulsating bubble surfactometer); efficacy in vivo (ie, in animal studies and human trials); absence of biologic toxicity of the surfactant, including each of its additives or components; and the ease and cost of preparation of the material. Notter[9] further designated those critical characteristics of exogenous surfactant for restoring the interfacial properties within the lung and commented on the pharmacologic properties necessary to decrease the work of breathing, increase alveolar stability on expiration, decrease pulmonary edema, and have uniform alveolar recruitment on inspiration.

Not all premature infants demonstrate evidence of surfactant deficiency or RDS.[10] Many trials have failed to recognize this fact. Numerous surveys have confirmed that RDS develops in only 60% to 80% of infants of less than 32 weeks' gestation, and fewer still require ventilatory intervention. Highly predictive tests of lung surfactant phospholipid "maturity" have existed since Gluck et al[11] introduced the lecithin/sphingomyelin (L/S) ratio. These tests were later refined by Hallman and Teramo[12] to include measurements of the acidic phospholipids (phosphatidylglycerol and phosphatidylinositol), and newer and more rapid tests are being developed to determine surfactant maturity status. Indeed, recent reports measuring the major surfactant-associated glycoprotein (the 35-kilodalton protein now called surfactant protein [SP] A) further enhance the predictive accuracy of these tests of antenatal or neonatal lung maturity.[13] It is unfortunate that these analyses have not been used in most clinical trials to discriminate those in whom RDS would never have developed (20% to 40% of the

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Accepted for publication Sept 26, 1988.

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sample size). Any surfactant preparation would demonstrate substantial positive effects if the infant did not have the disease that surfactant was intended to treat! For an adequate evaluation of whether a particular surfactant is efficacious when administered at or near birth, efforts must be undertaken to determine whether RDS would have developed before any claims of clinical improvement.

CRITICAL ASPECTS OF CLINICAL TRIAL DESIGN

Unlike most drugs used in neonatology, which have their efficacy and safety determined in adults or children prior to their use in infants, surfactant therapy has been introduced in infants with very low birth weights. To demonstrate statistical differences in outcome between surfactant treated and conventionally ventilated infants, of necessity the most vulnerable very preterm infants (and thus those most likely to benefit) have been the experimental subjects. These trials have generally been limited to infants of less than 30 to 32 weeks' gestation, although some trials of heterologous surfactant have excluded infants with a birth weight less than 750 g, even though this group makes up a sizable sample in other trials and poses a major challenge to neonatologists.

Since a preponderance of the data from clinical trials has favored surfactant therapy, it is reasonable to assume that all infants who are anticipated to have RDS (by lung maturity tests) or who manifest respiratory distress will eventually be candidates for exogenous surfactant instillation. However, several questions are unresolved and require investigation before the optimal preparation is available. For example, can surfactant be protein free, or are certain proteins (or peptides) necessary for optimal function in vivo? To what degree do the various preparations retard the "inhibiting" influences of serum proteins or other substances in the airways, and how can this be tested in infants?

Many critical questions remain unanswered. Is only transient improvement in respiratory function sufficient as an assessment of efficacy, or should outcome measures with longer-term follow-up be used, including death and/or bronchopulmonary dysplasia? Given a choice, what surfactant preparations should be administered, and by what objective criteria should regulatory agencies approve their use? The critical question for safety is how complete and what duration of follow-up should the pediatric community demand before these agents (or most other drugs used in neonatology) are released for widespread use? As with other drugs, once they are released, any licensed physician can use them. Should restrictions be placed on their recommended use? Who should administer them—neonatologists, pediatricians, obstetricians, nurse-midwives, neonatal nurses—and in what circumstances—at birth, after manifest respiratory distress confirmed by roentgenographic evidence that suggests RDS in selected preterm infants? At what lower limit for gestational age should this therapy be applied, and who should determine the limitations on the availability of what is likely to be an expensive drug? Furthermore, it has yet to be determined what methods of administration and what "styles" of ventilation have the optimal effect. Why are the effects dramatic in some units but not in others? This suggests that conventional ventilatory techniques, fluid therapy, approach to the patent ductus arteriosus, and a multitude of other practices strongly influence the effectiveness of surfactant treatment.

Animal studies have documented that surfactant instilled into the trachea is better distributed than surfactant given several minutes later, after assisted ventilation.[14] More recent studies have shown that when administered after birth, high-frequency oscillation superimposed on intermittent mandatory ventilation led to better oxygenation, better distribution of radiolabeled surfactant, and more uniform alveolar expansion.[15] However, high-frequency ventilation has not been widely used clinically in combination with surfactant.

Six surfactant preparations are currently being evaluated in North America in infants (human amniotic fluid surfactant at several centers and bovine surfactant in Toronto; calf lung surfactant extract [CLSE], developed in Rochester, NY, and also produced as Infasurf [ONY Inc, Buffalo]; surfactant TA [Abbott Laboratories, North Chicago, Ill]; and a synthetic surfactant [Exosurf, Burroughs-Wellcome, Research Triangle Park, NC]). In Europe, porcine surfactant (Curosurf, Chiesi Farmaceutici, Parma, Italy), surfactant TA, ALEC (Cambridge, England), and human amniotic fluid surfactant have been used. The natural, heterologous, and modified heterologous surfactants demonstrate a striking but variable alteration in oxygen requirements and ventilatory needs soon after intratracheal administration. Studies utilizing ALEC demonstrated that there is not an acute response, but there is evidence of a modest reduction in ventilatory needs about 18 hours after initial administration.[16] These results are summarized in Tables 1 and 2. Surfactant TA is now available for routine clinical use in Japan, and encouraging reports from China have documented the successful use of human amniotic fluid surfactant.

These preparations have been evaluated in clinical trials in conventionally ventilated infants of 23 to 34 weeks' gestation. Study designs have not always demanded that premature infants treated with surfactant have evidence of surfactant deficiency, and a variety of "placebo" agents have been used, including intratracheally administered saline in quantities that have been shown to worsen lung function in animal studies.[17] Noncontrolled "trials" or case registries have been undertaken on the basis of early favorable results, even though these earlier trials did not use precisely the same surfactant preparations and were inconclusive because they lacked statistical power. Surfactant therapy studies have embarked on trial designs evaluating both the postventilatory administration of surfactant in varying doses to reverse ventilatory failure "rescue" and prophylactic administration before or nearly simultaneously with the first breath. These trials have contrasted the ventilatory and oxygen support; roentgenographic resolution of RDS; neonatal morbidities, with an emphasis on pulmonary air-leak syndromes; occurrence of bronchopulmonary dysplasia or variously defined chronic lung disease; and death in infants treated with surfactant and those who underwent conventional ventilation.

Table 1.—Postventilatory (Rescue) Trials of Surfactant

Type of Surfactant	Source, y*	No. of Patients Given Surfactant	No. of Controls	Treatment Criteria†	Outcome‡
Surfactant TA (supplemented bovine homogenate)	Fujiwara, 1980	10	0	RDS	PaO_2 increased, $PaCO_2$ decreased, A-aO_2 decreased, 9 patients had PDA
	Fujiwara, 1981	19	"3" (uncontrolled)	RDS	PO_2/FiO_2 increased, FiO_2 decreased, incidence of PDA increased
	Fujiwara, 1984	20	10	RDS	A-aO_2 decreased, MAP decreased, chest roentgenograms improved
	Fujiwara, 1984	37	5	RDS	A-aO_2 decreased, FiO_2 decreased, chest roentgenograms improved, incidence of PDA increased
	Raju, 1987	17	13	MAP >8 mm Hg, A-aO_2 ≤0.25, age ≤6 h	FiO_2 decreased, A-aO_2 decreased, incidence of air leaks decreased, incidence of PDA increased, incidence of BPD increased
	Gitlin, 1987	18	23	Birth weight≥1000 g, <1500 IMV, age <8 h, FiO_2 ≥0.4	No. of days supplemental FiO_2 ≥0.4 decreased, No. of days O_2 was given decreased
	Horbar, 1988	78	81	Birth weight 750-1750 g	FiO_2 decreased, incidence of ventilatory support >48 h decreased
Bovine lung lavage extract	Smyth, 1981	3	0	Severe RDS	PaO_2 increased, FiO_2 decreased, chest roentgenograms improved
	Smyth, 1983	6	0	Not listed	A-aO_2 increased (24 h effect)

(Continued on p 1336.)

VARIATIONS IN SURFACTANT COMPOSITION

Results of studies using both type II cell cultures and intact fetal lungs indicate that SP A is critical in the feedback regulation of the reuptake, internalization, and secretion of surfactant phospholipids and surfactant proteins.[18] Furthermore, we have shown a protective effect of SP A against low-molecular-weight cationic inhibitors,[19] and Possmayer[20] demonstrated that the addition of SP A to lipid extract surfactants increases their biophysical activity, so that at low concentrations their surface tension properties are similar to those of natural surfactants. These reults suggest that surfactants that contain SP A are more advantageous. The pharmacokinetics of exogenously administered surfactants (eg, recycling of exogenous surfactant into de novo synthesis and surfactant clearance from the lung, and the secretion of endogenous surfactant) in preterm infants requires careful study. Jobe[21] reported, in preterm lamb fetuses and in 3-day-old rabbits, similar patterns of recovery in airway lavage for natural surfactant and surfactant TA, with minimal clearance and no apparent alteration in recycling or secretion pathways.

Surfactants have varied in their composition and in the presence of surfactant-associated proteins. The contribution of these surfactant proteins to surfactant function are the focus of intense research. Human amniotic fluid surfactant contains all the major surfactant proteins. Heterologous surfactants obtained by lipid extraction are devoid of the major surfactant protein, SP A; they contain various quantities of low-molecular-weight lipophilic proteins (SP B or SP C). Surfactant TA has been derived from homogenized cow lung and then supplemented with synthetic phospholipids and neutral lipids, while Curosurf uses porcine lung lavage extracted using organic solvents and separated using column chromography. It contains no neutral lipids.[22] Calf lung lavage lipid extracts are prepared at several sites and do not contain SP A; instead, they contain only 1% to 2% lipophilic protein.[23] The dosages used are based on phospholipid content, and they are given in doses varying from 60 to 200 mg (they are usually given per kilogram of birth weight). This has made the "potency" of different surfactants difficult to compare on a weight basis.

Although it was recognized that retreatment with human surfactant was necessary for a sustained response in about half of the infants treated, others chose to evaluate the effect of single-dose therapy. Most of these trials demonstrated a substantial, albeit tran-

Table 1.—Postventilatory (Rescue) Trials of Surfactant (cont)

Type of Surfactant	Source, y*	No. of Patients Given Surfactant	No. of Controls	Treatment Criteria†	Outcome‡
Porcine CK	Kobyashi, 1981	1	0	RDS	Chest roentgenograms improved, PaO_2/FiO_2 increased, $PaCO_2$ decreased
	Ohta, 1981	1	0	RDS	"Improvement"
	Nohara, 1983	6	0	RDS	PaO_2 increased in 4 patients, chest roentgenograms improved
Curosurf (porcine surfactant)	Berggren, 1984	4	0	Severe RDS	PO_2 increased, PCO_2 decreased, incidence of air leaks decreased
	Robertson, 1988	77	69	Severe RDS, Birth weight 700-2000 g	Incidence of death and BPD decreased
Human amniotic fluid	Hallman, 1983	6	6	Age <10 h, <29 wk gestation, L/S ratio ≤2.0, no PG	PO_2 increased, PCO_2 decreased, chest roentgenograms improved
	Hallman, 1985	25	28	Age <10 h, birth weight <1500 g, severe RDS, L/S ratio <2.0, no PG	Incidence of death and BPD decreased, incidence of air leaks decreased, No. of infants who required FiO_2 >0.3 at 30 d was decreased
	Lang, 1988	10	14	25-32 wk gestation; severe RDS; mean treatment time, 5.6 h	PaO_2 increased, FiO_2 decreased, $A\text{-}aO_2$ increased, MAP decreased
Synthetic phospholipids (ALEC)§	Milner, 1983	10	0	RDS	No effect
	Wilkinson, 1985	12	0	≤32 wk gestation, RDS	No effect, L/S ratio in tracheal fluid increased
	Weintraub, 1985	22	0	RDS, PIP ≥20 cm H_2O, FiO_2 >0.6	$PaCO_2$ decreased, PIP decreased, 8 patients died

*Some of these citations are to data that have been presented only in abstracts or that were provided to the authors in personal communications. A list of references is available from the authors on request.

†RDS indicates respiratory distress syndrome; MAP, mean arterial pressure; $A\text{-}aO_2$, alveolar-arterial oxygen gradient; IMV, intermittent mandatory ventilation; FiO_2, fraction of inspired oxygen; L/S ratio, lecithin/sphingomyelin ratio; PG, phosphatidylglycerol; and PIP, peak inspiratory pressure.

‡PaO_2 indicates arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; PO_2/FiO_2, ratio of oxygen pressure to fraction of inspired oxygen; PDA, patent ductus arteriosus; and BPD, bronchopulmonary dysplasia.

§ALEC indicates artificial lung expanding compound (consists of synthetic dipalmitoylphosphatidylcholine and PG in 7:3 proportion).

sient, improvement in the alveolar-arterial O_2 ratio, a reduction in mean airway pressure, a reduction in oxygen need, and a decrease in the frequency of air leaks. A reduction in overall mortality or deaths attributable to RDS was not substantiated when a single dose of about 100 mg/kg of surfactant TA or CLSE was used in multicenter trials[24-26]; in the European trial of single-dose surfactant TA, there was a higher incidence of periventricular-intraventricular hemorrhage.[27] Porcine surfactant is reported to be quite similar to human surfactant in terms of improvement in ventilatory function with a higher dose, and it has also been found to significantly reduce the occurrence of both bronchopulmonary dysplasia and mortality in infants who weigh 700 to 2000 g at birth (55% of live births had no bronchopulmonary dysplasia when Curosurf was used vs 26% of controls, $P<.01$).[28] Further trials are underway to determine the relative benefit of prophylactic vs rescue therapy using multidose therapy with human surfactant, surfactant TA, CLSE, and Curosurf. Infasurf has also been reported to reduce mortality in very-low-birth-weight infants of 23 weeks' gestation contrasted with historical comparison infants,[29] and it is being used in noncontrolled investigational treatments at several centers in the United States.

DETERMINANTS OF EFFICACY

While neonatologists understand that the early improvement in ventilatory indexes and oxygen requirement reported with most surfactants clearly has some benefit by reducing risk factors associated with pneumothorax, transient improvement without a salutary effect on survival or a reduction in the frequency or severity of bronchopulmonary dysplasia must continue to be viewed with some skepticism.

Table 2.—Prophylactic Surfactant Treatment

Type of Surfactant	Source, y*	No. of Patients Given Surfactant	No. of Controls	Treatment Criteria†	Outcome‡
Surfactant TA (supplemented bovine homogenate)	Soll, 1988	79	81	Birth weight 750-1250 g, intubated 4-37 min after birth	FiO_2 decreased, chest roentgenograms improved, patients who weighed 750-999 g responded better
	Horbar, 1988	38	46	Birth weight 750-1750 g	$A\text{-}aO_2$ increased, MAP decreased, incidence of IVH increased
Bovine lung lavage extract	Enhorning, 1985	39	33§	<30 wk gestation	Incidence of death decreased, incidence of IVH decreased, incidence of air leaks decreased
Calf lung surfactant extract	Shapiro, 1985	16	16	25-29 wk gestation	Severity of RDS decreased transiently
	Kendig, 1988	34	31	25-29 wk gestation	Severity of RDS decreased, incidence of air leaks decreased
Infasurf (calf lung surfactant extract)	Kwong, 1985	14	13	24-28 wk gestation	Severity of RDS was decreased at 48 h, FiO_2 decreased, ventilatory support was decreased
	Kwong, 1988	315	None	23-29 wk gestation	Incidence of death decreased
	Bloom, 1987	43 (Infasurf), 13 (human amniotic fluid)	30 (comparison infants)	24-31 wk gestation	Incidence of death decreased, incidence of PIE decreased, FiO_2 decreased
Human amniotic fluid	Merritt, 1986	31	29	24-29 wk gestation, L/S ratio ≤2.0, no PG	Incidence of death decreased, incidence of BPD decreased, incidence of air leaks decreased
Synthetic phospholipids (ALEC)‖	Morley, 1981	22	33‡	≤34 wk gestation	Incidence of death decreased
	Wilkinson, 1982	16	16	≤32 wk gestation, with resuscitation	No effect
	Milner, 1984	10	6	<34 wk gestation, needed intubation	No effect
	Morley, 1985	243	220	25-34 wk gestation	Incidence of death decreased before 30 wk
	Ten Centre Study Group, 1987	159	149	25-29 wk gestation	Mortality decreased, incidence of IVH decreased, hours of ventilation decreased
DPPC plus high-density lipoproteins	Halliday, 1984	49	51	25-33 wk gestation	No effect

*Some of these citations are to data that have been presented only in abstracts or that were provided to the authors in personal communications. A list of references is available from the authors on request.

†L/S ratio indicates lecithin/sphingomyelin ratio; PG, phosphatidylglycerol.

‡FiO_2 indicates fraction of inspired oxygen; $A\text{-}aO_2$, alveolar-arterial oxygen gradient; MAP, mean arterial pressure; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome; PIE, pulmonary interstitial emphysema; BPD, bronchopulmonary dysplasia; and DPPC, dipalmitoylphosphatidylcholine.

§There were more male infants among the controls than among the patients given surfactants.

‖ALEC indicates artificial lung expanding compound (consists of synthetic DPPC and PG in 7:3 proportion).

Guidelines of efficacy must be concerned not only with early improvements in ventilatory status (and reductions in factors contributing to the development of intraventricular hemorrhage and bronchopulmonary dysplasia) but should also require that these therapies actually improve the morbidity and mortality associated with RDS. Rigorous efficacy end points should also mandate that morbidities strongly correlated with an adverse neurodevelopmental outcome (severe grades of intraventricular hemorrhage, periventricular leukomalacia, severe bronchopulmonary dysplasia) should be reduced and certainly should not be increased. Dunn and coworkers[30] reported that surfactant therapy appears to shift some infants from death to a handicapped existence, while there was almost an equal number of normal survivors in the surfactant-treated and control groups. Using an artificial surfactant (ALEC), Morley[31] found a significant reduction in mortality in infants of less than 30 weeks' gestation, but he did not find a simultaneous increase in the frequency of hearing loss, cerebral palsy, or mental impairment among survivors. Vaucher et al[32] demonstrated improved neurodevelopmental performance among surfactant-treated infants and speculated that the decrease in the incidence of bronchopulmonary dysplasia should ultimately lead to improved long-term outcome. Surfactant treatment must also not be associated with specific untoward effects, such as allergic sensitization to foreign proteins, and it must not stimulate harmful immunologic reactions. These crucial immunologic data and completed follow-up studies are presently lacking for most of the surfactant preparations currently being tested throughout the world.

While demands for efficacy are essential, another consideration should be cost. In Japan, a single dose of surfactant costs the equivalent of $1000 (H. Togar, MD, written communication, July 22, 1988). Shennan and coworkers[33] analyzed the costs of neonatal intensive care based on the medical, nursing, and laboratory costs of infants with RDS. In infants of less than 27 weeks' gestation, while there was an improvement in survival, no decrease was seen in neonatal intensive care unit costs, while in infants of 27 to 29 weeks' gestation, savings of $7000 to $12 000 (Canadian) were observed. Halliday and associates[34] reported that with increased early survival, the intensive care nursery workload increased by nearly fourfold in total ventilation days, and there were similar increased demands for intensive care monitoring, parenteral nutrition, and nursing workload, and there was an even greater increase in total hospital days.

ASSESSMENT OF VARIOUS SURFACTANTS

With so many uncertainties in the broader application and availability of surfactant preparations, a logical approach would be to perform a multicenter international trial comparing the relative efficacy of each surfactant being considered for regulatory approval in each of several countries. Such a trial would provide a reference for the performance of various surfactants that have been developed and would show which ones have promise. Furthermore, as future generations of surfactants are developed based on recombinant or other technologies, it is critical to have a surfactant reference or "gold standard" against which to test these agents, since controlled trials comparing these agents with placebo would be difficult to justify. Such a comparison trial is consistent with our competitive yet cooperative spirit and encompasses prudent consumer activism that demands the best and safest possible products for the world's infants and our patients. It is imperative that each surfactant being considered for approval in the United States be evaluated side by side within the framework of an independent randomized trial sponsored by the National Institutes of Health, Food and Drug Administration, National Academy of Science, or another agency to determine the relative benefits (or harm) of various surfactants. As previous trials have not controlled for the multitude of variations in obstetrics, neonatology, and nursing practices (the use of glucocorticoid and tocolytic agents, ventilatory techniques, "weaning" guidelines, and nursing procedures, to name but a few) or for population differences, these clinical trials should encompass practices that are representative of perinatal-neonatal care. Such an approach would provide thoughtful pediatricians and parents with the knowledge base that should prevent a recurrence of recent tragedies associated with the premature approval of drugs for use in premature infants. Because several surfactants might be expected to demonstrate efficacy using the clinical end points previously discussed and assuming a power of 80% and a significance level of at least 5% (two-sided), the numbers of infants required to demonstrate significant changes in ventilatory measurements, air leaks, the occurrence of bronchopulmonary dysplasia, and RDS-associated mortality (eg, a reduction in 30% to 50% for each variable) by superior agents would probably require 100 to 120 infants in each treatment category. With multicenter cooperation it is quite possible that these data could be accrued within an 18-month period.

What arguments can be voiced in opposition to such a trial? Any clinical trial costs money, yet what is the value of our infants, who might be subjected to inferior treatments if such a comparison is not done? Such a trial might contradict previous trials and not clarify the issue of efficacy of a particular agent, but that is the risk of new knowledge. Some surfactant preparations may "work better" using various styles of ventilatory techniques (including oscillatory ventilation), fluid management, or other approaches not previously considered in trials (eg, following pharmacologic induction of lung maturity). Additional studies are needed to define how to optimize the effect of surfactant.

This is a promising era in neonatal-perinatal medicine, because dedicated basic and clinical investigators are focusing on the biology of the developing lung and on developmental pharmacology. Pediatricians should collect the wisdom of the past, not repeat previous errors, and demand the rigor of thorough evaluation of new techniques and therapies before they are put into widespread uncontrolled use. The role of a comparison trial in this regard is prudent medicine and sound clinical investigation, and it will ultimately benefit our patients by increasing our knowledge base of the effects and limitations of these powerful new surfactive agents.

This study was supported by the Sigrid Juselius Foundation, Helsinki; by grant HL35036 from the National Institutes of Health, Bethesda, Md; by grant 000112 from the Food and Drug Administration, Rockville, Md; and by the Finnish Academy, Helsinki.

References

1. *Forty Years of Achievement in Heart, Lung and Blood Research*, US Dept of Health and Human Services. Bethesda, Md, National Heart, Lung, and Blood Institute, 1987.
2. Avery ME, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. *AJDC* 1959;97:517-523.
3. Robillard E, Alarie Y, Dagenais-Perusse P, et al: Microaerosol administration of synthetic dipalmitoyl lecithin in the respiratory distress syndrome: A preliminary report. *Can Med Assoc J* 1964;90:55-57.
4. Chu J, Clements JA, Cotton EK, et al: Neonatal pulmonary ischemia: Clinical and physiologic studies. *Pediatrics* 1967;40:709-782.
5. Enhorning G, Robertson B: Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Pediatrics* 1972;50:58-66.
6. Adams FH, Towers B, Osher AB, et al: Effect of tracheal instillation of natural surfactant in premature lambs: Clinical autopsy findings. *Pediatr Res* 1978;12:841-848.
7. Fujiwara T, Maeta H, Chida S, et al: Artificial surfactant therapy in hyaline membrane disease. *Lancet* 1980;1:55-59.
8. Shapiro DL: The development of surfactant replacement therapy and the various types of re-

placement surfactants. *Sem Perinatol* 1988;12:174-179.

9. Notter RH: Biophysical behavior of lung surfactant: Implications for respiratory physiology and pathophysiology. *Sem Perinatol* 1988;12:180-212.

10. Collaborative Group on Antenatal Steroid Therapy: Effect of antenatal dexamethasone administration, in *Prevention of Respiratory Distress Syndrome*, US Dept of Health and Human Services publication (NIH) 85-2695. Bethesda, Md, National Institutes of Health, 1985.

11. Gluck L, Kulovich M, Borer RC, et al: The interpretation of lecithin/sphingomyelin ratio in amniotic fluid. *Am J Obstet Gynecol* 1974;120:142-154.

12. Hallman M, Teramo K: Amniotic fluid phospholipid profile as a predictor of fetal lung maturity in diabetic pregnancies. *Obstet Gynecol* 1979;54:707-711.

13. Hallman M, Arjomaa P, Mizumoto M, et al: Surfactant proteins in the diagnosis of fetal lung maturity: I. Predictive accuracy of the 35 kD protein, the L/S ratio, and phosphatidylglycerol. *Am J Obstet Gynecol* 1988;158:531-535.

14. Jobe A, Ikegami M, Jacobs H, et al: Surfactant and pulmonary blood flow distribution following treatment of premature lambs with natural surfactant. *J Clin Invest* 1984;73:848-856.

15. Walther FJ, Kuipers I, Gidding CEM, et al: A comparison of high-frequency oscillation superimposed onto back-up mechanical ventilation on the distribution of exogenous surfactant in premature lambs. *Pediatr Res* 1987;22:725-729.

16. Ten Centre Study Group: Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies. *Br Med J* 1987;294:961-966.

17. Egan EA, Notter RH, Kwong MS, et al: Natural and artificial surfactant replacement in premature lambs. *J Appl Physiol* 1988;55:875-883.

18. Wright JR, Clements JA: Metabolism and turnover of lung surfactant. *Am Rev Respir Dis* 1987;135:426-444.

19. Hallman M, Merritt TA, Arjomaa P, et al: Is it possible to enhance the therapeutic effect of exogenous natural surfactant in RDS? Read before the Third International Symposium Basic Research on Lung Surfactant, Marburg, West Germany, Sept 14, 1988.

20. Possmayer F: The role of the low molecular weight hydrophobic proteins in surfactant function. Read before the Third International Symposium Basic Research on Lung Surfactant, Marburg, West Germany, Sept 12, 1988.

21. Jobe A: Metabolism of endogenous surfactant and exogenous surfactants for replacement therapy. *Sem Perinatol* 1988;12:231-244.

22. Noack G, Berggren P, Curstedt T, et al: Severe RDS treated with the isolated phospholipid fraction of Natural Surfactant. *Acta Pediatr Scand* 1987;76:697-705.

23. Notter RH, Shapiro DL, Ohning B, et al: Biophysical activity of synthetic phospholipids combined with purified lung surfactant 6000 dalton apoprotein. *Chem Phys Lipids* 1987;44:1-17.

24. Kendig JW, Notter RH, Cox C, et al: A clinical trial of single dose surfactant replacement therapy at birth: Final analysis. *Pediatr Res* 1988;23:413A.

25. Horbar JD, Sutherland J, Phillip AGS, et al: Multicenter trial of single dose surfactant-TA (STA) for treatment of respiratory distress syndrome (RDS). *Pediatr Res* 1988;23:410A.

26. Soll, RF, Hoekstra R, Fangman J, et al: Multicenter trial of single dose surfactant TA (STA) for prevention of respiratory distress syndrome (RDS). *Pediatr Res* 1988;23:425A.

27. Horbar JD, Linderkamp O, Schachinger H: European trial of single dose surfactant TA (STA) for treatment of respiratory distress syndrome (RDS). *Pediatr Res* 1988;23:510A.

28. Soenningsen N, Robertson B, Andersson B, et al: Endotracheal administration of surfactant in very low birth weight infants with respiratory distress syndrome. *Crit Care Med* 1987;15:918-922.

29. Kwong MS, Egan EA: Routine use of Infasurf (calf lung surfactant extract) at birth for prematures ≤32 wks gestation. *Pediatr Res* 1988;23:415A.

30. Dunn MS, Shennan AT, Hoskins EM, et al: Two year follow-up of infants in a randomized trial with surfactant replacement for the prevention of neonatal respiratory distress syndrome. *Pediatrics* 1988;82:543-547.

31. Morley C: Results with artificial surfactant. Read before the Third International Symposium Basic Research on Lung Surfactant, Marburg, West Germany, Sept 14, 1988.

32. Vaucher YE, Merritt TA, Hallman M, et al: Neurodevelopmental and respiratory outcome in early childhood after human surfactant treatment. *AJDC* 1988;142:927-930.

33. Shennan AT, Markel F, Dunn M, et al: Cost effect on surfactant replacement in prematures: Pilot study. Read before the Symposium on Surfactant and Respiratory Tract, Lund, Sweden, June 4, 1988.

34. Halliday HL, McClure BG, Reid M, et al: The first 50 babies with severe hyaline membrane disease treated with Curosurf in Belfast. Read before the Fifth International Berlin Symposium on Infant Mortality, Berlin, Sept 5, 1988.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Juvenile Granulosa Cell Tumor of the Testis

Manuel Nistal, MD; Elena Redondo, MD; Ricardo Paniagua, PhD (*Arch Pathol Lab Med* 1988;112:1129-1132)

THE VINDICATION OF LACTOSE

Decreased lactase levels are not as common as once believed: lactose actually helps resolve diarrhea often attributed to formula intolerance

Background

Though it is still common practice for physicians to recommend a lactose-free formula for infants with chronic nonspecific or postinfectious diarrhea, studies demonstrate that lactose is rarely the offending agent. In fact, recent clinical evidence shows that formula containing lactose may actually be helpful in resolving diarrhea.

Lactose routinely excluded from soy-based formula without intrinsic cause

Acute gastroenteritis in infants is often followed by chronic diarrhea. Conventional treatment for this involves delaying the reintroduction of usual feedings, and often withholding cow's milk or milk-based formula. Soy-based formulas are often substituted to eliminate the suspect protein. These formulas also replace lactose with sucrose and/or corn syrup for the carbohydrate source; this once seemed a good idea because congenital lactase deficiency, now regarded as extremely rare,[1] was formerly thought to be common in infants.

Protein, not lactose, is agent in most formula intolerance: guilt by association?

Most cases of lactose intolerance are temporary, secondary to protein-induced gastroenteritis, and quickly resolve as soon as the offending protein is withdrawn.[2] Liu et al[3] demonstrated convincingly that most infants initially intolerant of both milk and lactose could tolerate lactose after milk protein was eliminated from the diet. Lactose seems to play a role in formula intolerance only when associated with an offending protein. Gerrard[2] found that infants with confirmed allergy to cow's milk protein showed no signs of lactose intolerance when returned to breast milk. Also, clinical experience suggests that human milk frequently is well tolerated when other foods are not,[4,5] even though the carbohydrate of breast milk is entirely lactose. Groothuis et al[6] found that lactose formula did not prolong mild gastroenteritis in infants, but that these infants recovered as quickly as those fed formulas containing sucrose or maltodextrin.

Lactose helps resolve diarrhea

The most recent data indicate that lactose may actually resolve some of the symptoms formerly attributed to lactose intolerance or protein intolerance.[7] Forty infants were chosen who, following an initial presentation of acute gastroenteritis, were diagnosed as having chronic diarrhea and, presumably, formula intolerance. The infants were divided into three groups and fed formulas that were identical except for the carbohydrate source. Within four days, improvement was observed in 86% of the infants fed the formula containing lactose, compared with only 20% and 19% of those fed maltodextrin- or sucrose-containing formulas.

Lactose vindicated

Lactose is the carbohydrate of breast milk, the ideal infant nutritional source, and aids in the absorption of calcium,[8] magnesium, and zinc.[9] It causes beneficial biochemical and microbiological changes in the lower parts of the intestine,[10] helps establish favorable colonic flora,[11] and its galactose portion may be important in the rapid formation of brain lipids.[12] As described above, lactose may also take part in a specific mechanism for the inhibition of water and electrolyte losses through the bowel.[7] This beneficial energy source should not be eliminated from infant formulas because of outdated misinformation. The American Academy of Pediatrics Committee on Nutrition clearly states that "The current data do not suggest that lactose be routinely eliminated from the diet of infants recovering from diarrhea."[8] While the apparent hypoallergenicity of soy-based formulas may seem to make them suitable for infants with a family history of atopy, they contain no lactose; a more desirable alternative is the lactose-containing GOOD START H.A.™ Iron Fortified Hypoallergenic Infant Formula recently developed by Carnation Nutritional Products. For a product monograph write Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

REFERENCES:

1. Williams CA: Metabolism of lactose and galactose in man. *Prog Biochem Pharmacol* 1986;21:219-247.
2. Gerrard JW: Cow's milk and breast milk, in Brostoff J, Challacombe SJ (eds): *Food Allergy and Intolerance.* Eastbourne, England, Ballière Tindall, 1987, pp 344-355.
3. Liu H-Y, Tsao MU, Moore BA, et al: Bovine milk protein-induced intestinal malabsorption of lactose and fat in infants. *Gastroenterology* 1967;54:27-33.
4. Klish WJ, cited by Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, p 277.
5. Finberg L, Harper PA, Harrison HE, et al: cited by Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, p 277.
6. Groothuis JR, Berman S, Chapman J: Effect of carbohydrate ingested on outcome in infants with mild gastroenteritis. *J Pediatr* 1986;108:903-906.
7. Donovan GK, Torres-Pinedo R: Chronic diarrhea and soy formulas: Inhibition of diarrhea by lactose. *Am J Dis Child* 1987;141:1069-1071.
8. Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, pp 116, 278.
9. Zeigler EE, Fomon SJ: Lactose enhances mineral absorption in infancy. *J Pediatr Gastroenterol Nutr* 1983;2(2):288-294.
10. Grüttner R: Qualitative aspects of carbohydrates in the nutrition of infants. *Monatsschr Kinderheilkd* 1974;122(suppl 5): 264-267.
11. Braun OH: The protective effect of human milk against infections and its potential causes. *Klin Padiatr* 1976;188(4):297-310.
12. Brady RO: Sphingolipidoses and other lipid metabolic disorders, in *Basic Neurochemistry*, ed 3. Boston, Little Brown & Co, 1981, pp 615-624.

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From Research to Relevance

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Purpose.—This section of *AJDC* will focus on significant research that has a high probability of being translated into clinical usefulness. It is an attempt to predict pediatric practice of the future.

Editorial Comment.—*Dr Sullivan presents an excellent review on oxidant radical injury in relation to the newborn. Because the preterm infant has a greater susceptibility to the effects of toxic oxygen species, Dr Sullivan suggests that this disorder be called "oxygen radical disease of prematurity." He proposes an interesting hypothesis and suggests ways it can be tested. This fascinating article is easy to read, and the reader will enjoy an increased understanding of the antioxidant systems.*—J.J.C., Jr.

Iron, Plasma Antioxidants, and the 'Oxygen Radical Disease of Prematurity'

Jerome L. Sullivan, MD, PhD

Oxygen radical injury may be a common pathogenic mechanism in several neonatal diseases. The list includes but is not limited to retinopathy of prematurity, bronchopulmonary dysplasia, subependymal and intraventricular hemorrhage, and necrotizing enterocolitis. The greater incidence of these disorders in preterm infants suggests that some aspect of prematurity increases susceptibility to the effects of toxic oxygen species. Saugstad[1] has proposed the term "oxygen radical disease in neonatology" to describe the apparent propensity of neonates to oxygen radical injury. Because of the greater incidence in preterm infants, perhaps a better name for this disorder would be "oxygen radical disease of prematurity." Saugstad's work emphasizes increased oxygen radical production associated with increased levels of hypoxanthine, especially following hypoxia. Although elevated hypoxanthine concentrations after hypoxia increase superoxide production in the presence of xanthine oxidase, this effect may not completely explain the selectivity of the proposed oxygen radical disease for premature infants. Premature infants have plasma hypoxanthine concentrations similar to those of term infants.[1]

A possible explanation for the occurrence of these disorders in prematurity is that preterm infants may have defects in one or more of the antioxidant systems that protect more mature infants and older children from oxygen radical injury. From a teleologic point of view, it is reasonable that preterm infants have less-effective antioxidant systems. Lower oxygen tensions in the intrauterine environment may allow survival with less-potent antioxidant systems. Hypotheses based on possible defects in antioxidant protection are attractive because administration of the deficient antioxidant may allow both verification of the hypothesis and preventive treatment, if the hypothesis is confirmed. Many proteins and other substances that occur in vivo have demonstrable antioxidant activity in vitro. These include superoxide dismutase, catalase, glutathione peroxidase, vitamin E, ascorbic acid, uric acid, ceruloplasmin, and apotransferrin. The relative importance of each component in vivo in health and disease remains unclear. Results of in vitro assays are of limited value in addressing this question.[2] Recent studies with vitamin E in retinopathy of prematurity illustrate this point. In vitro vitamin E is a potent, lipophilic, chain-breaking antioxidant. Vitamin E is also known to be at a relatively low concentration in the plasma of premature infants. These findings appear to be strong circumstantial evidence that the low vitamin E levels of premature infants predispose them to retinopathy of prematurity. However, it has been difficult to establish that pharmacologic augmentation of vitamin E levels in preterm infants protects them from retinopathy of prematurity.[3,4]

Little attention has been given to the possible importance of components whose antioxidant activities depend on interactions with iron.[5,6] Over 90% of the preventive antioxidant activity of plasma is associated with ceruloplasmin and transferrin.[7-9] As preventive antioxidants, these two proteins are 200 to 500 times more potent than vitamin E, compared on a molar basis.[7,8] The antioxidant activities of both proteins depend on their interactions with iron and may thus be called "iron-associated antioxidants." The antioxidant activity of ceruloplasmin resides in its ferroxidase activity.[9] As a ferroxidase, ceruloplasmin catalyzes the oxidation of ferrous to ferric iron. Oxidation to the ferric form may facilitate the binding of iron

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Accepted for publication Aug 30, 1988.

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to transferrin. Inhibition of this enzymatic activity abolishes the antioxidant activity of ceruloplasmin. With transferrin, it is the unsaturated form, apotransferrin, that possesses antioxidant activity.[7,8] Apotransferrin loses its antioxidant activity after binding two ferric ions. The antioxidant activity of uric acid may also be dependent on interactions with iron.[10]

There are two reasons for considering a role for ceruloplasmin and apotransferrin in protection against an oxygen radical disease of prematurity:

1. The plasma concentrations of both ceruloplasmin[11,12] and transferrin[13-15] are low by adult standards in term neonates and are even lower in premature infants. Exactly such a pattern would be expected for antioxidants of importance in the pathogenesis of the oxygen radical disease of prematurity.
2. The antioxidant activity of a mole of apotransferrin is abolished by incubation with two moles of ferric iron.[7,8] Shortly after birth, in both term and preterm infants, there are major perturbations in iron metabolism that result in substantial increases in transferrin saturation.[13-19] This phenomenon has the effect of neutralizing much of the antioxidant activity of transferrin.

ROLE OF IRON IN OXYGEN RADICAL INJURY

The role of iron in oxygen radical injury is the subject of a rapidly growing literature. Iron is thought to facilitate formation of the highly reactive hydroxyl radical (·OH) from superoxide in the Haber-Weiss reaction:

$$O_2^- + Fe^{3+} \rightarrow O_2 + Fe^{2+}$$
$$2O_2^- + 2H^+ \rightarrow O_2 + H_2O_2$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$$

An in vivo role for iron in oxygen radical injury is supported by studies that show protective effects of deferoxamine against this form of injury.[20-22] Deferoxamine-bound iron does not facilitate ·OH formation or lipid peroxidation. More recent studies have found that nutritional iron deficiency is also protective in several types of oxygen radical–mediated injury.[23-25]

NEONATAL IRON METABOLISM

Birth is a point of transition for the neonate from a relatively iron-rich environment in utero to the iron-poor extrauterine environment. In utero, iron is available from the mother in excess of needs. This is clearly the case, since normal neonates have iron in storage.[17] After birth, acquisition of enough additional iron to support maximal growth is not always assured.

Transition to the higher oxygen concentration of extrauterine existence is also associated with a virtual cessation of red blood cell formation that persists for six to eight weeks.[18,19] This adjustment has major effects on neonatal iron metabolism. Since red blood cell senescence and lysis continue or, in the presence of a hemolytic process, increase, there is an increase in the amount of iron that must be stored. The usual postnatal cessation in erythropoiesis appears to be a sufficient explanation for the large increases in transferrin saturation and plasma ferritin levels seen in both term and preterm infants shortly after birth. In the study of Siimes et al,[16] the median serum ferritin level in normal infants rose to a postnatal peak of 356 µg/L at 1 month of age and fell to 30 µg/L by 6 months of age.

In premature infants, much higher levels of serum ferritin may be seen, especially in infants who receive iron supplements or blood transfusions. The preterm infant, in part simply by virtue of being small, has a very limited capacity to assimilate exogenous iron. Premature infants also appear to have unregulated absorption of iron.[18] Their absorption of iron is proportional to dietary iron regardless of need. In those given supplemental iron or blood transfusions, Shaw[18] observed some very high values for serum ferritin (1000 to 2000 µg/L). In an adult, these values would suggest a diagnosis of homozygous hemochromatosis.

At birth, preterm infants have less total body iron than term infants, in part because of their smaller size. Premature delivery also interrupts iron acquisition from the mother during the period of maximal iron absorption. Despite the smaller total body iron pool, premature newborns also have very high transferrin saturations. Transferrin saturations of 1.00 (100%) may be encountered. This is a consequence of the low transferrin concentrations seen in premature infants. Transferrin concentration increases with gestational age and correlates closely with gestational age. Regulation of the transferrin level in preterm neonates may thus be determined more by developmental factors than by iron status.[13,19]

Ceruloplasmin in Preterm Infants

The other plasma protein with iron-associated antioxidant activity is ceruloplasmin. The antioxidant activity of ceruloplasmin depends on its ferroxidase activity, as noted above. Acting as a ferroxidase, it may exert some of its antioxidant activity by facilitating the binding of iron to transferrin. However, even in the absence of transferrin, ceruloplasmin is a potent antioxidant.[9] Recent studies suggest that iron is most effective in promoting lipid peroxidation when ferric and ferrous ions are present in equal concentrations. Ferric iron alone is much less effective than an equimolar 1:1 mixture of ferric and ferrous iron.[26] Ceruloplasmin may thus have an antioxidant effect by increasing the ferric/ferrous ratio.

The plasma concentration of ceruloplasmin is lower in premature than in term infants.[9,11,12] Even in fully mature infants, the ceruloplasmin concentration at birth is only about one third of that seen in older children and adults. There is also evidence that preterm infants with respiratory distress syndrome have lower cord serum ceruloplasmin concentrations than unaffected preterm infants.[27]

HYPOTHESIS

The following hypothesis is proposed: Premature infants are abnormally susceptible to oxygen radical injury because of developmentally low levels of the iron-associated antioxidant proteins ceruloplasmin and transferrin combined with postnatal changes in iron metabolism that decrease the concentration of apotransferrin.

The hypothesis suggests that the oxygen radical disease of prematurity is primarily a disorder of iron-associated antioxidant deficiency. It also implies that, in some premature infants, a state of clinically significant iron overload develops in the first few weeks of life. This is not to say that the iron present in the infant is excessive in terms of the amount required for erythropoiesis and growth. Rather, the available iron overloads the infant's limited iron-handling capacity.

The hypothesis does not exclude an important role for other factors in the pathogenesis of an oxygen radical disease of prematurity. In particular, at the present level of understanding, it does not explain why injury is more prominent in the retina of one infant and in the lungs of another. Additional factors must be acting to determine which site of injury predominates in a given case.

VERIFICATION

Several testable predictions arise from the hypothesis, the most significant of which involve possible modes of preventive therapy. Existing data on iron metabolism, ceruloplasmin, and transferrin in the neonatal period generally support the proposed hypothesis.[11-19] These data provide indirect evidence, for example, of an inverse association between the mean transferrin level and disease incidence. Verification of the hypothesis will require demonstration of such an association in individual patients. The hypothesis suggests that disease should occur significantly more frequently in those infants with low ceruloplasmin levels, high transferrin saturation, and/or high ferritin levels. Verification will require studies of ceruloplasmin levels, transferrin saturation, and ferritin levels in relation to the occurrence of disease in a series of premature infants. Positive results in such studies should be followed by an attempt to prevent disease occurrence by pharmacologic augmentation of ceruloplasmin and/or apotransferrin levels in premature infants.

ANTIOXIDANT ACTIVITY AND PLASMA TRANSFUSION

One additional implication of the hypothesis requires further comment, since it has potential importance both in verification and in possible preventive therapy. Intravenous administration of purified preparations of ceruloplasmin and apotransferrin should increase the antioxidant activity of an infant's plasma. These are not standard pharmaceutical products. However, ceruloplasmin and apotransferrin are often routinely given to sick newborns in the form of donor plasma. Since adult donor plasma has greater concentrations of these two proteins than that of term and, especially, preterm neonates, transfusion of donor plasma can potentially increase the infant's plasma levels of ceruloplasmin and apotransferrin.

It is useful to estimate the maximum potential increase in these levels. Ceruloplasmin in, for example, the plasma of a woman donor who uses oral contraceptives can exceed 1000 mg/L.[9] In preterm infants, levels of less than 100 mg/L are not uncommon.[9] Thus, a blood donor's plasma may contain more than ten times as much ceruloplasmin per volume. If this woman donor were also a frequent donor, it is possible that she could be iron depleted or even marginally iron deficient because of her high donation frequency. Frequent blood donors are at risk of iron deficiency.[28] Since iron deficiency is known to be associated with an elevated plasma transferrin concentration and decreased transferrin saturation,[29] her apotransferrin level may be significantly higher than the normal adult level. Since a preterm infant's apotransferrin level may be essentially zero, ie, in infants having a transferrin saturation of 1.00, the adult woman blood donor's plasma apotransferrin concentration may exceed that of a premature infant by several orders of magnitude.

The calculation of maximum possible differences between donor plasma and preterm infant plasma is germane to this discussion, because, in attempting preventive therapy, ceruloplasmin and apotransferrin levels in donor plasma can be readily measured by widely available laboratory tests before transfusion. Donor plasma can be selected to assure maximal augmentation of an infant's iron-associated antioxidant activity. If the proposed hypothesis is correct, plasma transfusion may be an effective preventive therapy against oxygen radical injury.

ANTIOXIDANT ACTIVITY AND BLOOD TRANSFUSION

These considerations raise the question of the role of blood transfusions in this disorder. It has been suggested that blood transfusion may increase an infant's risk.[5] Can blood transfusion augment an infant's iron-associated antioxidant activity? It might appear that transfusion of blood containing some adult plasma could increase the infant's iron-associated antioxidant activity. That this is an unlikely consequence of blood transfusion is shown by the following calculations.

A typical 10 mL transfusion of packed red blood cells may contain as much as 3 g of hemoglobin. Since hemoglobin contains approximately 60 μmol of iron per gram, 10 mL of packed red blood cells may contain as much as 180 μmol of iron. Plasma does not typically have a total iron-binding capacity greater than 80 μmol/L. In 10 mL of packed red blood cells with not more than 5 mL of plasma, there should be no more than 0.4 μmol of plasma total iron-binding capacity. Therefore, packed red blood cells may easily contain 450 times as much hemoglobin iron as the plasma total iron-binding capacity. The data of Shaw[18] indicate that blood transfusions may result in a net addition to storage iron in preterm infants. Even small amounts of packed red blood cells contain amounts of iron that are large in relation to the premature infant's total body iron. A 1000 g premature infant has only about 50 mg of total body iron, or only about five times that contained in a single 10 mL transfusion of packed red blood cells.[5]

DEFEROXAMINE AS AN ANTIOXIDANT

Administration of deferoxamine is one possible approach to increasing both iron-binding capacity and antioxidant activity. Use of deferoxamine in preventing retinopathy of prematurity has been proposed.[5] Deferoxamine chelates ferric iron and has been shown to protect against various forms of oxygen radical–mediated injury in vivo.[20-22]

In premature infants, deferoxamine may prove to be effective in boosting antioxidant activity in the short term.

However, long-term treatment with deferoxamine may be of limited usefulness in this setting. Deferoxamine-bound iron in plasma is not retained by the kidneys. Repeated use of deferoxamine could exhaust a small infant's modest store of iron. In contrast, the addition of exogenous human apotransferrin to an infant's plasma should augment plasma antioxidant activity without facilitating urine iron loss.

MILK AND THE ANTIOXIDANT ACTIVITY OF APOLACTOFERRIN

Lactoferrin is a transferrinlike iron-binding protein present in highest concentration in milk and neutrophils.[30] In the antioxidant activity assay of Stocks and coworkers,[7,8] both purified apolactoferrin and human milk have substantial antioxidant activity (J.L.S. and R. B. Newton, PhD, unpublished observations, 1987). Human apolactoferrin given intravenously to rats has been shown to protect them in a dose-dependent manner against acute lung injury in vivo in a complement and neutrophil–dependent model system.[20]

Breast-fed premature infants may have a lower incidence of retinopathy of prematurity.[31] Within the context of the proposed hypothesis, an explanation for this observation is suggested. Human milk is rich in lactoferrin, almost all of which is normally free of iron.[32,33] Colostrum is particularly rich in lactoferrin. Since premature infants can absorb large amounts of intact milk macromolecules into their plasma,[34] it is possible that apolactoferrin may be absorbed from milk in amounts sufficient to boost plasma antioxidant activity. A positive effect on neonatal antioxidant protection could be another of the many benefits infants derive from breast-feeding.

CONCLUSION

Developmentally low levels of ceruloplasmin and transferrin together with postnatal changes in iron metabolism that increase transferrin saturation may leave some premature infants with very low levels of iron-associated antioxidant protection. It is proposed that deficiency in the iron-associated antioxidants increases susceptibility to oxygen radical–mediated injury in the retina, lung, brain, and intestine. Increased vulnerability to injury may lead to the development of retinopathy of prematurity, bronchopulmonary dysplasia, subependymal and intraventricular hemorrhage, or necrotizing enterocolitis. The hypothesis can be verified by demonstrating increased disease incidence in those premature infants with the greatest deficiencies in iron-associated antioxidants and by successful preventive therapy with exogenous ceruloplasmin and/or apotransferrin.

References

1. Saugstad OD: Hypoxanthine as an indicator of hypoxia: Its role in health and disease through free radical production. *Pediatr Res* 1988;23:143-150.
2. Dormandy TL: Free-radical oxidation and antioxidants. *Lancet* 1978;1:647-650.
3. Phelps DL, Rosenbaum AL, Isenberg SJ, et al: Tocopherol efficacy and safety for preventing retinopathy of prematurity: A randomized, controlled, double-masked trial. *Pediatrics* 1987;79:489-500.
4. Hittner HM, Speer ME, Rudolph AJ, et al: Retrolental fibroplasia and vitamin E in the preterm infant: Comparison of oral versus intramuscular:oral administration. *Pediatrics* 1984;73:238-249.
5. Sullivan JL: Retinopathy of prematurity and iron: A modification of the oxygen hypothesis. *Pediatrics* 1986;78:1171-1172.
6. Sullivan JL: Serum antioxidant activity in neonates. *Arch Dis Child* 1988;63:748-750.
7. Stocks J, Gutteridge JMC, Sharpe RJ, et al: Assay using brain homogenate for measuring the antioxidant activity of biological fluids. *Clin Sci* 1974;47:215-222.
8. Stocks J, Gutteridge JMC, Sharp RJ, et al: The inhibition of lipid autoxidation by human serum and its relation to serum proteins and α-tocopherol. *Clin Sci* 1974;47:223-233.
9. Gutteridge JMC, Stocks J: Caeruloplasmin: Physiological and pathological perspectives. *CRC Crit Rev Clin Lab Sci* 1981;14:257-329.
10. Davies KJA, Sevanian A, Muakkassah-Kelly SF, et al: Uric acid–iron ion complexes: A new aspect of the antioxidant functions of uric acid. *Biochem J* 1986;235:747-754.
11. Hilderbrand DC, Fahim Z, James E, et al: Ceruloplasmin and alkaline phosphatase levels in cord serum of term, preterm, and physiologically jaundiced neonates. *Am J Obstet Gynecol* 1974;118:950-954.
12. Buffone GJ, Brett EM, Lewis SA, et al: Limitations of immunochemical measurement ceruloplasmin. *Clin Chem* 1979;25:749-751.
13. Scott PH, Berger HM, Kenward C, et al: Effect of gestational age and intrauterine nutrition on plasma transferrin and iron in the newborn. *Arch Dis Child* 1975;50:796-798.
14. Galet S, Schulman HM, Bard H: The postnatal hypotransferrinemia of early preterm newborn infants. *Pediatr Res* 1976;10:118-120.
15. Saarinen UM, Siimes MA: Developmental changes in serum iron, total iron-binding capacity, and transferrin saturation in infancy. *J Pediatr* 1977;91:875-877.
16. Siimes MA, Addiego JE, Dallman PR: Ferritin in serum: Diagnosis of iron deficiency and iron overload in infants and children. *Blood* 1974;43:581-590.
17. Brittenham GM, Danish EH, Harris JW: Assessment of bone marrow and body iron stores: Old techniques and new technologies. *Semin Hematol* 1981;18:194-221.
18. Shaw JCL: Iron absorption by the premature infant: The effect of transfusion and iron supplements on the serum ferritin levels. *Acta Paediatr Scand* 1982;299(suppl):83-89.
19. Lukens JN: Iron metabolism and iron deficiency anemia, in Miller DR, Baehner RL, McMillan CW, et al (eds): *Blood Diseases of Infancy and Childhood.* St Louis, CV Mosby Co, 1984, pp 115-146.
20. Ward PA, Till GO, Kunkel R, Beauchamp C: Evidence for role of hydroxyl radical in complement and neutrophil-dependent injury. *J Clin Invest* 1983;72:789-801.
21. Babbs CF: Role of iron ions in the genesis of reperfusion injury following successful cardiopulmonary resuscitation: Preliminary data and a biochemical hypothesis. *Ann Emerg Med* 1985;14:777-783.
22. Editorial: Metal chelation therapy, oxygen radicals, and human disease. *Lancet* 1985;1:143-145.
23. Sullivan JL, Till GO, Ward PA: Iron depletion decreases lung injury after systemic complement activation, abstract. *Fed Proc* 1986;45:452.
24. Andrews FJ, Morris CJ, Lewis EJ, et al: Effect of nutritional iron deficiency on acute and chronic inflammation. *Ann Rheum Dis* 1987;46:859-865.
25. Chandler DB, Barton JC, Briggs DD, et al: Effect of iron deficiency on bleomycin-induced lung fibrosis in the hamster. *Am Rev Respir Dis* 1988;137:85-89.
26. Braughler JM, Duncan LA, Chase RL: The involvement of iron in lipid peroxidation: Importance of ferric to ferrous ratios in initiation. *J Biol Chem* 1986;261:10282-10289.
27. Omene JA, Longe AC, Ihongbe JC, et al: Decreased umbilical cord serum ceruloplasmin concentrations in infants with hyaline membrane disease. *J Pediatr* 1981;99:136-138.
28. Finch CA, Cook JD, Labbe RF, et al: Effect of blood donation on iron stores as evaluated by serum ferritin. *Blood* 1977;50:441-447.
29. Herbert V: Recommended dietary intakes (RDI) of iron in humans. *Am J Clin Nutr* 1987;45:679-686.
30. Nemet K, Simonovits I: The biological role of lactoferrin. *Haematologia* 1985;18:3-12.
31. Cunningham AS: Breast-feeding, antioxidants, and retinopathy of prematurity. *Am J Obstet Gynecol* 1987;156:1040-1041.
32. Siimes MA, Vuori E, Kuitunen P: Breast milk iron-A declining concentration during the course of lactation. *Acta Paediatr Scand* 1979;68:29-31.
33. Fransson GB, Lönnerdal B: Iron in human milk. *J Pediatr* 1980;96:380-384.
34. Jakobsson I, Lindberg T, Lothe L, et al: Human α-lactalbumin as a marker for macromolecular absorption. *Gut* 1986;27:1029-1034.

The Effect of Testosterone Therapy on Spontaneous Growth Hormone Secretion in Boys With Constitutional Delay

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• Testosterone treatment is known to improve growth hormone (GH) secretion in boys with constitutional delay (CD). To determine whether spontaneous GH secretion is normal after treatment, we assessed GH secretion before and after a four- to five-month course of testosterone enanthate in eight adolescents with CD. Before testosterone therapy, the mean (±1 SD) 24-hour integrated concentration of GH (IC-GH) by constant blood withdrawal technique was 1.7±1.0 μg/L (normal range for age, 3.2 to 11.5 μg/L), and the IC-testosterone was 1.8±2.7 nmol/L. Two patients restudied during treatment had normal IC-GH values. After testosterone treatment, the mean IC-GH of the entire group was 3.3±2.6 μg/L, and the IC-testosterone was 6.5±5.3 nmol/L. Five of eight patients had IC-GH values that were again subnormal. A subnormal IC-GH associated with CD may persist after testosterone therapy is discontinued. Deficiency of spontaneous GH secretion may contribute to short stature and slower growth rates in this patient group. Whether GH therapy in these patients would have a beneficial effect on final height is unknown.

(*AJDC* 1988;142:1345-1348)

Constitutional delay (CD) in boys is characterized by slow growth, short stature, delayed pubertal development, and retarded osseous maturation.[1,2] These patients frequently undergo diagnostic growth hormone (GH) evaluation because the clinical signs of CD resemble the presentation of GH deficiency. If these patients with CD receive no pretest hormonal priming, the GH response to stimulation is often comparable with that of children with GH deficiency.[2-6] Priming with testosterone can lead to normal GH responses in patients with CD who initially exhibited deficient GH secretion.[2-6] These observations led to recommendations for inclusion of testosterone priming before GH stimulation testing in boys of pubertal age.[2,7]

The 24-hour integrated concentration of GH (IC-GH) gives an assessment of spontaneous GH secretion. The IC-GH by constant withdrawal of blood may be a more sensitive method for identifying patients with GH deficiency than traditional pharmacologic stimulation tests alone.[8-12]

The IC-GH in untreated patients with CD may be very low and has also been found to increase during testosterone therapy.[13,14] To our knowledge, the status of spontaneous GH secretion in patients with CD after testosterone treatment has not been previously evaluated. Using the method of constant blood withdrawal, we measured 24-hour IC-GH in patients with CD before and after a short therapeutic course of testosterone injections.

METHODS

The patients reported in this study were referred to the Division of Pediatric Endocrinology at the University of Maryland, Baltimore, for evaluation of delayed puberty and slow linear growth. Nonendocrine causes of short stature and delayed puberty were ruled out by patient history, physical examination, and standard laboratory studies. All patients were chemically euthyroid. All studies were performed at the University of Maryland. Procedures complied with institutional standards regarding the participation of human subjects. Informed consent was obtained from patients and parents before each diagnostic study.

Growth hormone response to provocative stimulation was assessed by testing with the following paired pharmacologic agents: insulin[15] and levodopa,[16] arginine hydrochloride,[15] or clonidine hydrochloride.[17] Spontaneous GH secretion was evaluated by determining the 20- to 24-hour IC-GH. Blood was obtained by a constant withdrawal technique through a nonthrombogenic catheter.[9,10,18] The IC-GH was determined in a pooled sample from the individual aliquot samples obtained every half hour as previously described.[9,10,13,18]

Growth hormone was assayed by a standard double-antibody technique.[19] Specific human GH antibody was obtained for the study from the National Hormone and Pituitary Program, Baltimore, Md.

Using the method outlined above, we previously reported IC-GH values for children aged 7 to 18 years having normal height, weight, and growth rates that ranged from 3.2 to 11.5 μg/L.[9,18]

Integrated concentrations of plasma testosterone were determined from the 20- to 24-hour pooled sample obtained from the constant withdrawal of blood for the determination of the IC-GH. Testosterone concentration was determined by a solid-phase radioimmunoassay in unextracted heparinized plasma.

In each case, the patient's primary physician recommended a short course of testosterone therapy. Patients began testosterone therapy within four weeks of their first diagnostic testing. Patients received testosterone enanthate, 200 mg intramuscularly, once a month for four to five months. Patients were clinically reevaluated after completion of testosterone injections. Repeated determinations for IC-GH and IC-testosterone were performed no sooner than six weeks after the last dose

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Accepted for publication Aug 15, 1988.

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Table 1.—Clinical Characteristics of Patients at Time of the First (Pretestosterone) and Second (Posttestosterone) Tests for Growth Hormone Secretory Capacity

Patient No.	Chronologic Age, y		Bone Age, y		Height, cm		Weight, kg		Growth rate, cm/y		Tanner Stage[21]	
	First	Second	First	Second	First	Second	First	Second	First	During	First	Second
1	15.7	16.2	12.0	13.0	156.7	162.8	66.3	67.7	2.2	12.2	P1G1	P3G3
2	15.2	15.9	11.0	12.0	142.1	149.6	36.3	41.4	3.2	12.0	P1G1	P2G3
3	14.7	15.6	13.5	. . .	155.5	163.5	39.0	47.0	4.0	8.0	P2G1	P4G3
4	14.7	15.7	13.0	14.0	141.9	151.6	33.0	41.0	4.0	11.1	P1G2	P3G3
5	15.6	16.1	13.5	14.0	161.4	168.8	49.9	59.7	3.8	11.3	P1G2	P4G4
6	15.5	16.5	13.5	. . .	159.3	168.1	66.0	81.0	4.0	9.9	P3G2	P5G4
7	16.9	18.25	12.5	14.0	160.0	172.0	60.0	72.0	4.0	12.2	P1G2	P4G3
8	16.1	16.75	13.0	. . .	153.5	160.3	42.0	51.0	5.2	8.9	P3G3	P4G4
Mean ± 1 SD	15.6 ± 0.7	16.4 ± 0.9	12.8 ± 0.9	13.4 ± 0.9	154.0 ± 7.0	162.0 ± 8.0	49.0 ± 14.0	58.0 ± 15.0	3.8 ± 0.9	10.7 ± 1.6	. . .	. . .

Table 2.—Laboratory Assessment of Growth Hormone (GH) and Testosterone in Patients Before (First Test) and After (Second Test) Testosterone Enanthate Therapy

Patient No.	Peak GH to Stimulation, μg/L		IC-GH, μg/L*			IC-Testosterone, nmol/L		
	First	Second	First	During	Second	First	During	Second
1	6.7	17.2	0.1	. . .	2.2	0.3	. . .	5.0
2	8.9	14.1	2.8	. . .	9.1	0.1	. . .	0.6
3	10.0	. . .	1.2	. . .	1.5	0.1	. . .	1.5
4	19.0	. . .	1.2	. . .	1.4	1.2	. . .	5.8
5	8.1	18.0	1.9	. . .	3.9	0	. . .	1.7
6	0.2	8.1	2.1	4.1†	0.7	4.0	27.3	13.0
7	6.8	23.0	1.0	5.8†	1.8	0.7	66.7	10.0
8	16.5	. . .	3.0	. . .	4.7	7.6	. . .	14.2
Mean ± 1 SD	10.3 ± 4.8	16.1 ± 5.5	1.7 ± 1.0	. . .	3.3 ± 2.6	1.8 ± 2.7	. . .	6.5 ± 5.3

*Normal range of integrated concentration of GH (IC-GH), 3.2 to 11.5 μg/L in children of normal stature aged 7 to 18 years.[18]

†Levels after retesting of patients 6 and 7 during testosterone therapy.

‡Statistically higher than level from first test, $P<.005$.

of testosterone. Patients who initially had stimulated GH levels less than 10 μg/L before testosterone therapy also underwent repeated pharmacologic stimulation tests then. The IC-GH was determined for patients 6 and 7 in midcourse of their testosterone therapy.

Patient heights were measured on a stadiometer. Pretreatment growth rates were reported from the interval approximately six months before therapy. Bone age was determined from roentgenograms of the hand according to the standards of Greulich and Pyle.[20] Pubertal development was assessed using methods described by Tanner.[21]

Differences in variables before and after therapy were assessed by paired *t* test.[22,23]

RESULTS

The chronologic age, bone age, height, weight, growth rate, and Tanner stage are given in Table 1 for the patients before and after testosterone therapy. In response to testosterone therapy, all patients had a marked improvement in pubertal development and growth rate ($P<.0004$).

The IC-testosterone and IC-GH before and after therapy are given in Table 2 for each patient. The mean IC-testosterone of the group after therapy was significantly higher ($P<.005$) than the pretreatment level.

Patients 3, 4, and 8 had normal GH responses to stimulation before testosterone therapy. Patients 1, 2, 5, and 7 had normal GH responses to stimulation after testosterone therapy. Only patient 6 had deficient GH responses to stimulation before and after testosterone therapy.

The pretreatment IC-GH values of all the patients were in the GH deficiency range of less than 3.2 μg/L.[9] After testosterone therapy, patients 2, 4, and 8 were found to have normal IC-GH values; however, the remaining five patients again had IC-GH values in the deficient range. Patients 6 and 7 had normal IC-GH values during testosterone therapy that reverted into the deficient range after testosterone therapy. Although IC-GH values after therapy tended to be higher than pretreatment levels, this difference was not statistically significant ($P<.1$) in the eight patients studied. There was no correlation between the posttreatment IC-GH and the IC-testosterone.

COMMENT

We previously reported normative values for the 24-hour IC-GH from a pooled sample obtained by the constant blood withdrawal method.[18] The

IC-GH is highest in the pubertal and early adult years and declines thereafter with increasing age.[18] The pediatric subjects in that report were all of normal height, weight, and growth rate, and their IC-GH values ranged from 3.2 to 11.5 µg/L.[18]

The method of constant blood withdrawal for determination of the IC-GH has been used to study poorly growing children who had GH deficiency diagnosed as a GH response to paired pharmacologic stimulation below 10 ng/mL. These patients with deficient GH responses to stimulation all had subnormal IC-GH values of 3.2 µg/L or less.[9]

Using the same techniques, we subsequently demonstrated the existence of a subgroup of poorly growing children who have normal GH responses to stimulation but subnormal IC-GH values.[9] Replacement doses of GH result in improved growth similar to that for patients with deficient GH response to pharmacologic stimulation.[10] Other investigators using somewhat different methods for determining the IC-GH reported similar experiences.[8,11,12]

Spontaneous GH secretion may have an important role in mediating normal growth and puberty in the adolescent age group. The combination of high endogenous GH secretion together with rising testosterone levels may be necessary for the normal adolescent growth spurt in boys.[24] Growth hormone secretion in adolescence may mediate the concentration of sex hormone–binding globulin, which, in turn, may influence testosterone effect and the progression of puberty.[25]

It has been suspected that inadequate secretion of GH contributes to the clinical manifestations of CD, particularly poor linear growth.[2] Even before the age of adolescence, boys with CD may have deteriorating growth and delayed osseous maturation that is clinically similar to the presentation of GH deficiency.[1,2] If testosterone priming is not performed, a large portion of patients with CD will have impaired GH secretion.[2-6] Bierich[12] found that adolescent patients with CD without testosterone priming had subnormal spontaneous GH levels, and treatment with GH alone led to a marked improvement in growth rate.

A hallmark of CD has been the substantial improvement in stimulated GH secretion brought about by exogenous testosterone.[2-6] We previously reported that testosterone therapy substantially increases the IC-GH.[13] During testosterone therapy, patients with CD who initially had subnormal IC-GH values were found on repeated examination to have IC-GH values in the normal range.[14] In our study, the two patients (6 and 7) who were reevaluated during testosterone therapy had normal IC-GH values.

In response to a short course of testosterone therapy, patients with CD also have an impressive acceleration of linear growth, with greater advancement in height age than bone age, enhanced predicted adult height, pubertal development, and improved self-image and social relationships.[26] The acute salutary changes in GH secretion and growth rate during testosterone therapy suggested a previously untested hypothesis that spontaneous GH secretion will be normal once androgen treatment ends. However, we found that once testosterone therapy is stopped, IC-GH values in patients with CD again tended to be in the subnormal range. Increases in the IC-GH values into the normal range observed during testosterone therapy are not predictive of a normal IC-GH after testosterone therapy. As yet, we do not have sufficient long-term follow-up data on our patients with CD to assess the effect of a low IC-GH on their subsequent linear growth or final adult height.

Wilson et al,[27] in a follow-up study of patients with CD treated only with testosterone, reported the mean final height of treated patients as 171.2 ± 4.6 cm, or −0.9 SDs below the mean height of the adult male population. Patients with CD who did not receive testosterone had a lower but not statistically different mean height from treated patients. As a group, the patients with CD in their report[27] had a final height significantly shorter than the reference population, whether treated or untreated. Courses of testosterone therapy longer than four or five months do not seem to increase the final height of patients with CD.[28] Therefore, factors in addition to lack of testosterone or delayed onset of puberty may lead to the significantly shorter adult height of patients with CD. It is possible that deficient spontaneous GH secretion may be one factor causing the shorter final height in this group of patients.

Our findings suggest that decreased spontaneous GH secretion is associated with CD and that subnormal spontaneous GH secretion may recur even after a successful short course of testosterone therapy. It remains to be determined whether GH replacement in patients with CD with subnormal IC-GH values would have a beneficial effect on final adult height.

References

1. Wilkins L: Delay in the onset of adolescent growth and development, in *The Diagnosis and Treatment of Endocrine Disease in Childhood and Adolescence*, ed 3. Springfield, Ill, Charles C Thomas Publishers, 1965, p 164.
2. Prader A, Zachman M, Bucher H: Constitutional delay of growth and puberty: Auxological and endocrine characteristics, in Cacciari E, Prader A (eds): *Pathophysiology of Puberty*. Orlando, Fla, Academic Press, 1980, pp 123-135.
3. Martin LG, Clark JW, Connor TB: Growth hormone secretion enhanced by androgens. *J Clin Endocrinol Metab* 1968;28:425-428.
4. Deller JJ, Boulis MW, Harris WE, et al: Growth hormone response patterns to sex hormone administration in growth retardation. *Am J Med Sci* 1970;259:292-295.
5. Illig R, Prader A: Effect of testosterone on growth hormone secretion in patients with anorchia and delayed puberty. *J Clin Endocrinol Metab* 1970;30:615-618.
6. Martin LG, Grossman MS, Connor TB, et al: Effects of androgens on growth hormone secretion and growth in boys with short stature. *Acta Endocrinol* 1979;91:201-212.
7. *Human Growth Hormone Application Forms: Guidelines, Oct 28, 1981*. Baltimore, National Hormone and Pituitary Program.
8. Spiliotis BE, August GP, Hung W, et al: Growth hormone neurosecretary dysfunction: A treatable cause of short stature. *JAMA* 1984;251:2223-2230.
9. Zadik Z, Chalew SA, Raiti S, et al: Do short children secrete insufficient growth hormone? *Pediatrics* 1985;76:355-360.
10. Chalew SA, Raiti S, Armour KA, et al: Therapy in short children with subnormal integrated concentrations of growth hormone. *AJDC* 1987;141:1195-1198.
11. Albertsson-Wikland K, Hall F: Growth hormone treatment in short children: Relationship between growth and serum insulin-like growth factor I and II levels. *J Clin Endocrinol Metab* 1987;65:671-678.
12. Bierich JR: Treatment of constitutional

delay of growth and adolescence with growth hormone. *Klin Padiatr* 1983;195:309-316.

13. Thompson RG, Plotnick L, Kowarski AA, et al: The pubertal growth spurt: Role of human growth hormone, in Raiti S (ed): *Advances in Human Growth Hormone Research,* US Dept of Health, Education, and Welfare publication (NIH) 74-619. US Dept of Health, Education, and Welfare 1973, pp 670-694.

14. Link K, Blizzard RM, Evans WS, et al: The effect of androgens on the pulsatile release and the 24-hour mean concentration of growth hormone in prepubertal males. *J Clin Endocrinol Metab* 1986;62:159-164.

15. Raiti S, Davis WT, Blizzard RM: A comparison of the effects of insulin hypoglycemia and arginine infusion on the release of human growth hormone. *Lancet* 1967;2:1182-1183.

16. Weldon VV, Gupth SK, Haymond W, et al: The use of L-dopa in the diagnosis of hyposomatotropism in children. *J Clin Endocrinol Metab* 1973;36:42.

17. Lanes R, Hurtado E: Oral clonidine—an effective growth hormone–releasing agent in prepubertal subjects. *J Pediatr* 1982;100:710-714.

18. Zadik Z, Chalew SA, McCarter RS, et al: The influence of age on the 24 hour integrated concentration of growth hormone. *J Clin Endocrinol Metab* 1985;60:513-516.

19. Schalch DS, Parker ML: A sensitive double antibody immunoassay for human growth hormone in plasma. *Nature* 1964;203:1141-1145.

20. Greulich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of Hand and Wrist.* Stanford, Calif, Stanford University Press, 1959.

21. Tanner JM: *Growth at Adolescence.* Boston, Blackwell Scientific Publications Inc, 1962.

22. Ray AA (ed): *SAS User's Guide: Statistics.* Cary, NC, SAS Institute, Inc, 1982.

23. Zar JH: *Biostatistical Analysis,* ed 2. Englewood Cliffs, NJ, Prentice-Hall International Inc, 1984.

24. Zachmann M, Prader A: Anabolic and androgenic effect of testosterone in sexually immature boys and its dependency on growth hormone. *J Clin Endocrinol* 1970;30:85-95.

25. Belgorosky A, Martinez A, Domene H, et al: High serum sex hormone–binding globulin (SHBG) and low serum non-SHBG-bound testosterone in boys with idiopathic hypopituitarism: Effect of recombinant human growth hormone treatment. *J Clin Endocrinol Metab* 1987; 65:1107-1111.

26. Rosenfeld RG, Northcraft GB, Hintz RL: A prospective, randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. *Pediatrics* 1982;69:681-687.

27. Wilson DM, Fei J, Hintz R, et al: Effects of testosterone therapy for pubertal delay. *AJDC* 1988;142:96-99.

28. Martin MM, Martin ALA, Mossman FL: Testosterone treatment of constitutional delay in growth and development: Effect of dose on predicted versus definitive height. *Acta Endocrinol* 1986;113(suppl):147-152.

Librarian's Note.—*See also:* Wilson DM, Kei J, Hintz RL, et al: Effects of testosterone therapy for pubertal delay (*AJDC* 1988;142:96-99); correction (*AJDC* 1988;142:286).

Quotables:

Words of comfort, skillfully administered, are the oldest therapy known to man.

LOUIS NIZER
Perspectives in Biology and Medicine 1985

Percutaneous Nephrostogram in the Newborn With Bilateral Renal Cystic Disease

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• Percutaneous antegrade pyelography should be considered in the few, select, critically ill newborns with bilateral renal cystic disease when the diagnosis is critical to management and difficult with the usual imaging procedures. Two extremely ill newborns with severe oliguria and cystic abnormalities in both kidneys by ultrasound underwent sonographic guidance for percutaneous antegrade nephrostograms in the first week of life. With injection of contrast medium, definitive diagnoses were made of a multicystic dysplastic kidney on one side and an obstructed hydronephrotic kidney on the other, thereby directing decompression of the obstructed kidney to preserve native renal function. This procedure can provide a definitive diagnosis in these rare but difficult cases.

(*AJDC* 1988;142:1349-1351)

The two most common causes of an abdominal mass in the newborn are a multicystic dysplastic kidney (MDK) and hydronephrosis.[1,2] The initial imaging of an abdominal mass is often done with ultrasound, a particularly useful method since it does not depend on renal function. Though sonographic criteria for differentiation of MDK from hydronephrosis have been developed,[3] distinguishing MDK from severe hydronephrosis can occasionally be difficult in the newborn.[4,5] In those instances where the infant has one normal kidney or renal function is normal, diagnosis is not urgent. However, in the rare patient in whom both kidneys are abnormal and renal function is severely depressed, it is important to make the distinction between a dysplastic condition such as MDK and an obstructed hydronephrotic kidney that may be surgically correctable. An obstructed hydronephrotic kidney, even with a thin rim of parenchyma, may be salvaged surgically.[2]

Bilateral MDKs in a live newborn are rare. In one reported series of 44 patients with MDK, seven (16%) had contralateral hydronephrosis from ureteropelvic junction obstruction, and only two patients (4%) had a bilateral MDK.[6] A definitive diagnosis of obstructive hydronephrosis or MDK in each kidney when both are severely abnormal can guide surgical intervention to the most salvageable kidney in these ill patients.

PATIENTS AND METHODS

Two critically ill newborns had bilateral cystic abdominal masses on sonography (Figs 1, top left and top right, and 2, left and middle). Nuclear medicine studies were not performed because of severely diminished renal function. There was marked oliguria. One 3-day-old infant underwent both percutaneous nephrostograms in one session. The other infant had the nephrostograms at 5 and 7 days of age. In each patient, on each side, the procedure was performed with the nonsedated patient lying prone on the radiographic table with heaters to maintain temperature. After immobilizing the infants, the cystic masses were localized under real-time sonography (5-MHz transducer). With sterile technique, a 22-gauge needle was placed into each cystic mass with sonographic confirmation of the needle position. Fluid was aspirated and sent for analysis. Iothalamate meglumine (Conray 17%) was injected under fluoroscopic control. The distinguishing criteria included communicating cysts, central pelvis, presence of a ureter, and contrast in the bladder. Roentgenograms documented the contrast in the systems.

RESULTS

Patient 1

The ultrasound scan (Fig 1, top left and top right) of the first ill infant suggested a single large cyst on the right without identifiable renal parenchyma. The group of cysts on the left appeared to communicate, and the largest was central; the configuration was similar to a dilated central collecting system. No ureters were seen. We concluded, with the clinical evidence of severe renal compromise, that the more normal kidney was on the left, probably an obstruction of the ureteropelvic junction. The cyst on the right without appreciable renal cortex was believed to be the less functioning kidney.

At 5 days of age, percutaneous punctures with 22-gauge needles on the left revealed noncommunicating cysts (Fig 1, bottom left) with no identifiable collecting system or ureter, changing the diagnosis to left MDK.

Two days later, because of a very small but continued urine output, the right side was punctured. Figure 1, bottom right, shows injection of the percutaneous nephrostomy tube, subsequently placed, which revealed anatomic details similar to those seen fluoroscopically at the time of percutaneous needle puncture. The right kidney was hydronephrotic, obstructed at the ureteropelvic junction.

The patient went on to need long-term peritoneal dialysis and a kidney transplant.

Patient 2

Sonograms of the kidneys in this sick 3-day-old infant revealed multiple cystic structures of varying size that did not appear to communicate in each

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Accepted for publication Aug 19, 1988.

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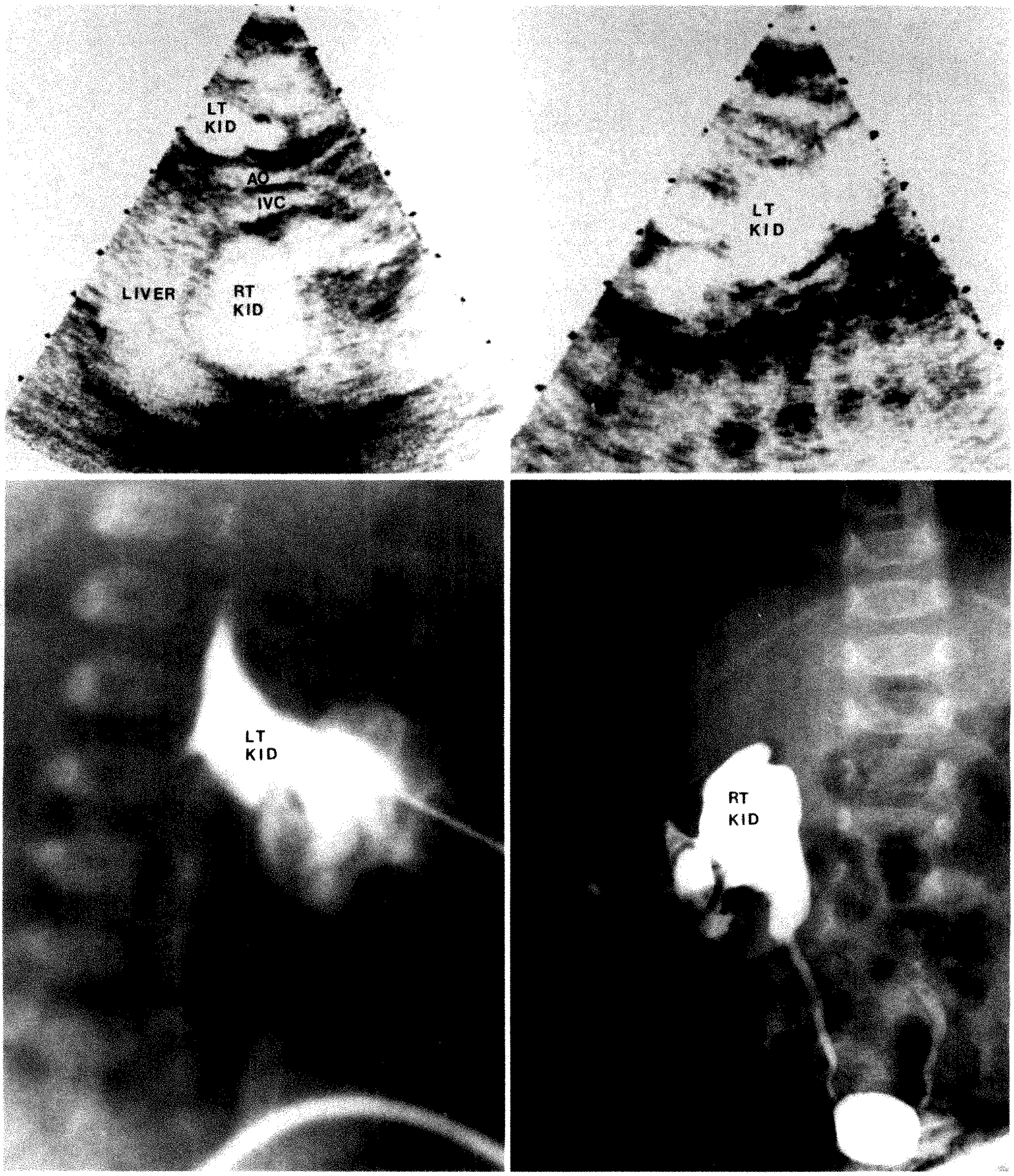

Fig 1.—Top left, Coronal ultrasound scan of patient 1, with aorta (AO) and inferior vena cava (IVC) visualized. Single cyst in right kidney (RT KID) below liver and cysts in left kidney (LT KID) are identified. Top right, Coronal ultrasound scan of left kidney showing collection of cysts that resembled a collecting system. This was multicystic dysplastic kidney (MDK). Bottom left, After several percutaneous punctures and filling of isolated cysts, this spot film confirms left MDK. Bottom right, Percutaneous injection of right system shows right hydronephrosis, right ureter, and bladder filling with reflux into the atretic distal left ureter.

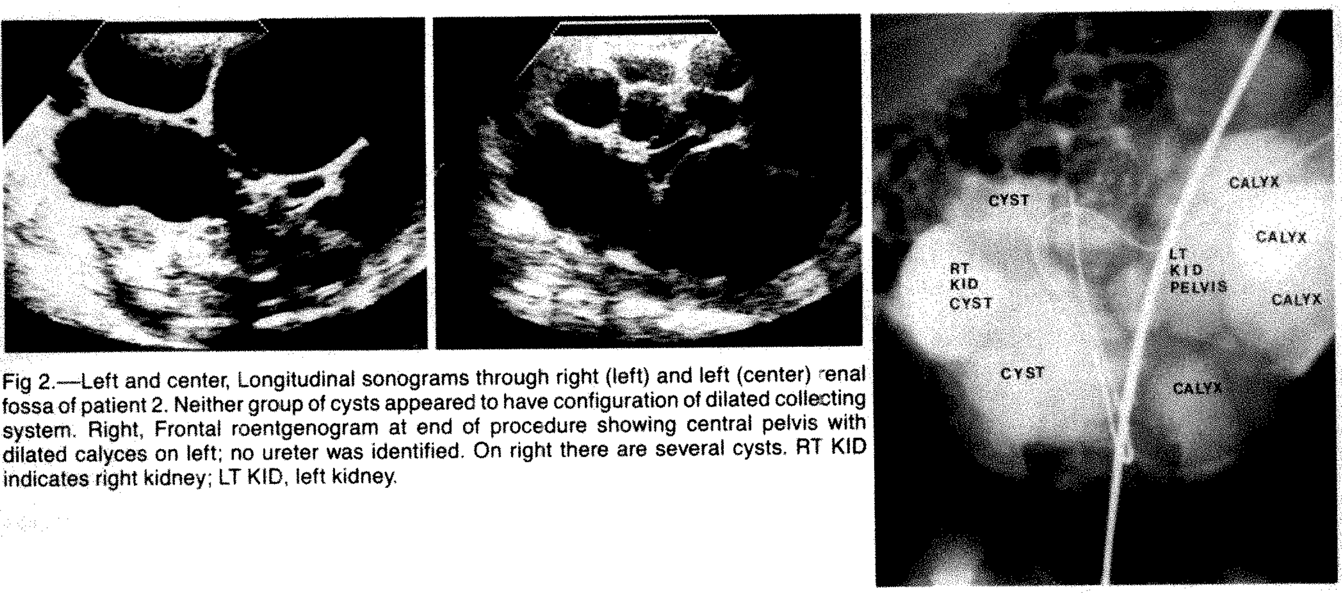

Fig 2.—Left and center, Longitudinal sonograms through right (left) and left (center) renal fossa of patient 2. Neither group of cysts appeared to have configuration of dilated collecting system. Right, Frontal roentgenogram at end of procedure showing central pelvis with dilated calyces on left; no ureter was identified. On right there are several cysts. RT KID indicates right kidney; LT KID, left kidney.

renal fossa (Fig 2, left and middle). The infant did have some urine output, suggesting that the underlying problem might be severe but incomplete obstruction.

Percutaneous puncture of the left side showed communicating cysts with a larger central one, suggesting an obstruction of the ureteropelvic junction (Fig 2, right). No contrast was identified in the bladder or a ureter. A percutaneous nephrostomy tube was placed, and some urine was drained over the next week.

The right side was punctured several times, and several cysts filled with contrast. Only two of the cysts communicated. A tube was placed but failed to drain urine over the next week.

The patient eventually needed long-term peritoneal dialysis and received a renal transplant.

COMMENT

Infants with severe bilateral renal disease are critically ill, usually oliguric or anuric with respiratory distress. Any procedure, and certainly surgery, constitutes a significant risk in such children. However, early delineation of the renal anatomy is obviously important to decide if there is a surgical lesion that needs to be corrected urgently. Percutaneous nephrostomy was first described in a child in 1865.[7] Renal puncture in the neonatal period has been described with the intravenous pyelogram used for guidance[8]; however, poor renal concentrating ability in the neonate and, in these cases with severe underlying renal disease, no concentrating ability preclude such a study. Ultrasound does not rely on renal function and can provide details of renal anatomy in these patients. However, as documented in the literature, even in the most capable hands there are pitfalls in these diagnoses.[4,5] In our first case, the sonographic evaluation (Fig 1) led us to suspect the left kidney to be the better functioning one, since it appeared to have more of a collecting system and more cortex than the right kidney, where little cortex was identified and there was one large cystic structure. The percutaneous nephrostogram more clearly demonstrated the renal anatomy, correcting the sonographic interpretation (Fig 1). An attempt to place a nephrostomy tube under fluoroscopy failed, and surgical decompression with a single flank incision confirmed an obstruction of the ureteropelvic junction on the right. The second patient had percutaneous nephrostomy tubes placed during the procedure.

Percutaneous nephrostography for more detailed delineation of renal anatomy is a procedure to be considered in very select circumstances. These include critically ill newborns with severe bilateral renal cystic disease when the diagnosis is critical to management and difficult with the usual imaging modalities. When an obstructed hydronephrotic collecting system is demonstrated, percutaneous placement of a draining tube can facilitate the immediate management of these sick children.

References

1. Felson B, Cussen LJ: The hydronephrotic type of unilateral congenital multicystic disease of the kidney. *Semin Roentgenol* 1975;10:113-123.
2. Bloom DA, Brosman S: The multicystic kidney. *J Urol* 1978;120:211-215.
3. Stuck KJ, Koff SA, Silver TM: Ultrasonic features of multicystic dysplastic kidney: Expanded diagnostic criteria. *Radiology* 1982;143:217-221.
4. Wood BP, Goske M, Rabinowitz R: Multicystic renal dysplasia masquerading as ureteropelvic junction obstruction. *J Urol* 1984;132:972-974.
5. Sanders RC, Hartman DS: The sonographic distinction between neonatal multicystic kidney and hydronephrosis. *Radiology* 1984;151:621-625.
6. Griscom NT, Vawter GF, Fellers FX: Pelvoinfundibular atresia: The usual form of multicystic kidney: 44 unilateral and two bilateral cases. *Semin Roentgenol* 1975;10:125-131.
7. Bloom DA, Morgan RJ, Scardino PL: Thomas Hillier and percutaneous nephrostomy. *Urology*, in press.
8. Saxton HM, Cameron JS, Chantler C, et al: Renal puncture in infancy. *Br Med J* 1973;3:267-270.

Increased Cytosol Aminopeptidase and Lactate Dehydrogenase in Serum Originating From Lymphocytes in Measles and Rubella Infection

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• We determined cytosol aminopeptidase (c-AP; EC 3.4.11.1) and lactate dehydrogenase (LDH) levels in serum; these enzymes are known to originate from lymphocytes in patients with measles and rubella. In patients with measles (n = 19), both enzyme levels increased markedly with the onset of rash: mean (± SD) c-AP was 269.7 ± 103.5 U/L and LDH was 1149.5 ± 255.2 U/L. In patients with rubella, activities of both enzymes increased mildly: c-AP (n = 18) was 81.6 ± 24.4 U/L and LDH (n = 13) was 674.0 ± 168.8 U/L. Increased c-AP and LDH levels in patients with measles and rubella presumably originate from the destruction of infected, activated lymphocytes, especially T lymphocytes.
(*AJDC* 1988;142:1352-1355)

We have recently reported that in patients with measles, a virus that is known to infect lymphocytes, activities of cytosol aminopeptidase (c-AP; EC 3.4.11.1) and lactate dehydrogenase (LDH) in serum are markedly increased and that presumably these enzymes originate from lymphocytes.[1,2]

Although the enzyme LDH is widely distributed among tissues in humans, it has been shown to originate from human lymphocytes.[3] Ringoir and Plum[4] reported that LDH_3 was the most important fraction in lymphocytes. However, cases with increased serum LDH that originated from lymphocytes have been reported infrequently, mostly from patients with lymphoid malignant neoplasms.[5,6] Recently, it was shown that patients with acquired immunodeficiency syndrome or acquired immunodeficiency syndrome–related complex demonstrated significant elevation of serum LDH activity, suggesting an association between uncontrolled B-lymphocyte proliferation and elevated serum LDH activity.[7,8]

Cytosol aminopeptidase is a cytosolic enzyme that preferentially hydrolyzes natural substances, like L-leucine amide and L-leucylglycine, and must be distinguished from microsomal aminopeptidase (EC 3.4.11.2).[9] Measurement of microsomal aminopeptidase (so-called LAP activity) in human serum originally was introduced as an aid in the diagnosis of diseases of the hepatobiliary tract.[5] In contrast, c-AP is primarily located in the cytosol of liver cells, and its activity in serum is thought to be a useful indicator of liver cell damage.[9] In recent years, it has been shown that c-AP is also contained in human lymphocytes[10] and that aminopeptidase activity may play an important role in the regulation of lymphocyte activation.[11]

However, other than our report,[2] only a few articles have been published concerning clinical cases of patients with increased c-AP in serum that is of possible lymphocytic origin. An increase in serum c-AP activity was found to be associated with malignant lymphoma, leukemia, and generalized lymphadenitis.[12,13] The purpose of this study was to investigate increases in c-AP and LDH levels in the serum of patients with measles and rubella and to compare the levels of these enzyme activities between these two groups of patients.

PATIENTS AND METHODS

Patients With Measles

We determined c-AP, LDH and its isozymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and γ-glutamyl transferase (GGT) at one- to five-day intervals in 19 patients with measles (mean age, 2.8 ± 2.7 years). Of the 19 patients, ten were hospitalized with respiratory complications: two with pneumonia, seven with bronchitis, and one with laryngitis. Eight of the ten patients with respiratory complications were presented in our previous report.[2] The remaining nine patients had no complications.

In all patients, the complement fixation titers for measles demonstrated a fourfold or greater increase. In all patients, we measured acute and convalescent complement fixation titers of influenza A and B, adenovirus, respiratory syncytial virus, and *Mycoplasma pneumoniae*, in addition to the hemagglutination inhibition titers of parainfluenza virus types 1 to 3, but we were unable to demonstrate significant changes.

Patients With Rubella

Early in 1987, a rubella epidemic occurred in Japan. Between February and June 1987, hemagglutination inhibition titers for rubella demonstrated a fourfold or greater increase in 241 patients at the pediatric outpatient department of Nippon Kokan Hospital, Kawasaki, Japan.

We measured c-AP, LDH and its iso-

Accepted for publication Aug 10, 1988.

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Table 1.—Biochemical Data of Patients With Measles Infection*

Patient	AST	ALT	c-AP	LDH	LDH$_1$	LDH$_2$	LDH$_3$	LDH$_4$	LDH$_5$
1	78	17	482	1194	25.9	30.3	34.0	7.2	2.4
2	57	20	461	1262	17.0	31.9	37.7	6.4	7.1
3	67	18	407	1266	. . .	. . .	. . .	. . .	. . .
4	66	21	405	1520	15.3	29.6	38.4	12.1	4.7
5	68	20	330	1180	14.5	30.8	38.9	11.3	4.5
6	88	39	298	1168	. . .	. . .	. . .	. . .	. . .
7	67	27	281	1079	25.9	26.9	33.8	9.0	4.2
8	67	15	266	907	. . .	. . .	. . .	. . .	. . .
9	70	22	255	1987	17.3	31.0	34.1	13.1	4.5
10	65	30	248	1026	13.9	27.7	34.8	16.0	7.6
11	60	22	244	1091	. . .	. . .	. . .	. . .	. . .
12	60	17	238	901	22.0	30.2	30.8	12.1	5.0
13	55	19	237	777	15.6	30.1	39.3	12.5	2.5
14	57	15	223	1157	14.2	27.8	39.5	16.7	1.8
15	72	24	184	1075	. . .	. . .	. . .	. . .	. . .
16	62	23	168	1247	14.9	30.9	36.4	14.4	3.4
17	41	10	142	942	. . .	. . .	. . .	. . .	. . .
18	65	46	130	1042	. . .	. . .	. . .	. . .	. . .
19	67	15	125	1019	. . .	. . .	. . .	. . .	. . .
Mean ± SD	64.8 ± 9.3	22.1 ± 8.4	269.7 ± 103.5	1149.5 ± 255.2	17.9 ± 4.4	29.7 ± 1.5	36.2 ± 2.7	11.9 ± 3.2	4.3 ± 1.7

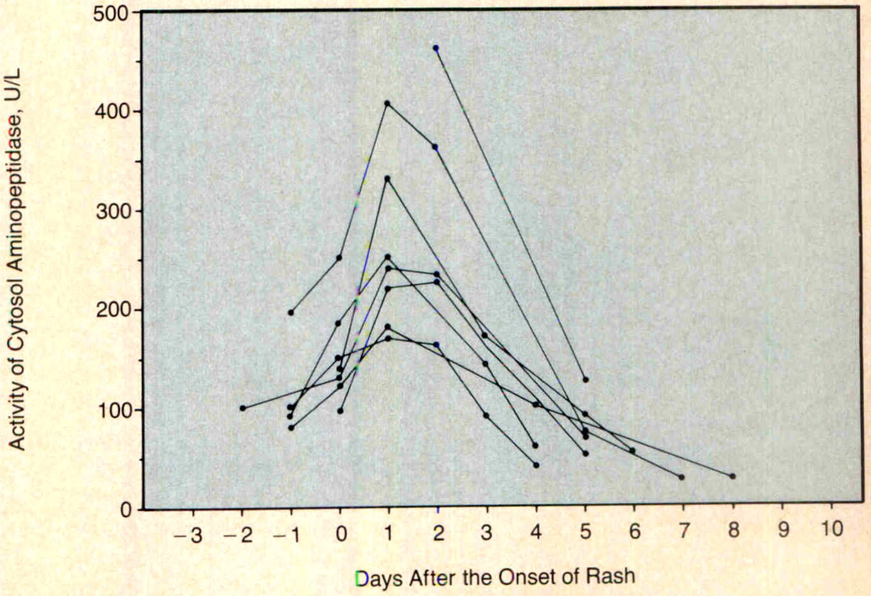
*All values are given in units per liter. AST indicates aspartate aminotransferase (normal, 20 to 50 U/L); ALT, alanine aminotransferase (normal, 10 to 40 U/L); c-AP, cytosol aminopeptidase (normal, 25 to 60 U/L); and LDH, lactate dehydrogenase (normal, 250 to 520 U/L). The highest values during the course of measles are seen with c-AP and LDH. The AST and ALT measurements are from the same day as the c-AP measurement.

zymes, AST, ALT, AP, and GGT at the first visit in all patients. Because ALT activity exceeded 50 U/L in 28 of the 241 patients, there was a possible association with hepatic dysfunction.[14] Therefore, we excluded these patients and analyzed the remaining 213 patients (mean age, 6.5 ± 2.8 years).

Measurements of Serum Enzymes

Cytosol aminopeptidase was measured by the method described by Sugiyama et al[15] that employed L-leucine amide as a substrate. In this method, nicotinamide-adenine dinucleotide phosphate–dependent glutamate dehydrogenase from *Proteus inconstans* is linked, simultaneously detecting ammonia liberated by aminopeptidase activity. Liberated ammonia is measured continuously by the decreased optical density at 340 nm caused by the oxidation of the reduced form of nicotinamide-adenine dinucleotide phosphate.[9] The other enzymes were determined with a sequential, multichannel, continuous-flow analyzer by well-established methods.[16,17]

Reference intervals are c-AP, 25 to 60 U/L; LDH, 250 to 520 U/L; AST, 20 to 50 U/L; and ALT, 10 to 40 U/L. Reference intervals for LDH isozymes in children at our hospital are LDH$_1$, 20.7% to 39.5%; LDH$_2$, 26.9% to 42.1%; LDH$_3$, 20.1% to 31.3%; LDH$_4$, 2.3% to 11.7%; and LDH$_5$, 2.0% to 9.1%. Data were expressed as the mean ± SD.



Changes in serum cytosol aminopeptidase activity in eight patients with measles infection.

RESULTS
Activity of c-AP and LDH in Patients With Measles

Activities of serum enzymes in the 19 patients with measles are shown in Table 1. Cytosol aminopeptidase activity was markedly increased in all patients: the mean peak value of c-AP was 269.7 ± 103.5 U/L, with a range from 125 to 482 U/L. In five patients (26.3%), it was greater than 300 U/L, an unusually high level.

Lactate dehydrogenase activity was also markedly increased to 1149.5 ± 255.2 U/L and ranged from 777 to 1987 U/L. When the total LDH level peaked, a significant increase in

Table 2.—Biochemical Data of Patients With Rubella Infection*

Days	No. of Patients	AST	ALT	c-AP	LDH	LDH$_1$	LDH$_2$	LDH$_3$	LDH$_4$	LDH$_5$
0	43	33.0 ± 8.3	16.2 ± 7.2	60.0 ± 12.6	389.5 ± 80.3	26.3 ± 4.0	31.4 ± 2.3	25.4 ± 2.9	11.0 ± 2.6	6.0 ± 1.8
1	111	32.9 ± 7.6	16.0 ± 7.2	65.6 ± 21.3	420.9 ± 99.1	24.0 ± 4.5	30.5 ± 2.5	27.6 ± 3.5	12.0 ± 2.9	6.0 ± 2.1
2	39	39.2 ± 8.4	18.7 ± 8.4	76.4 ± 29.7	573.8 ± 137.5	20.1 ± 4.2	28.7 ± 3.4	31.6 ± 3.0	13.8 ± 3.4	6.1 ± 2.0
3	18	43.8 ± 10.4	19.4 ± 4.9	81.6 ± 24.4	634.8 ± 131.9	16.9 ± 4.4	27.2 ± 1.8	34.5 ± 3.8	15.8 ± 3.2	6.3 ± 1.5
4	13	40.3 ± 8.6	21.5 ± 7.2	76.4 ± 30.2	674.0 ± 168.8	16.5 ± 5.1	30.0 ± 2.6	35.5 ± 4.5	13.6 ± 3.1	4.4 ± 0.8

*Values, given in units per liter, are mean ± SD. AST indicates aspartate aminotransferase (normal, 20 to 50 U/L); ALT, alanine aminotransferase (normal, 10 to 40 U/L); c-AP, cytosol aminopeptidase (normal, 25 to 60 U/L); and LDH, lactate dehydrogenase (normal, 250 to 520 U/L).

levels of LDH$_3$ and LDH$_4$, with LDH$_3$ predominating, was characteristic; the LDH$_5$ level was normal.

Alanine aminotransferase activity was within the normal range in all patients. Aspartate aminotransferase activity was slightly increased when both c-AP and LDH peaked. Activities of AP and GGT were normal in all patients.

Cytosol aminopeptidase activity gradually began to increase during the prodromal phase and rapidly increased with the appearance of rash, peaking in one to two days. Then it fell precipitously, returning to the normal range four to six days after the onset of rash (Figure).

Likewise, LDH activity slowly increased during the prodromal phase and increased rapidly with the appearance of rash; it peaked one to three days after the onset of rash. However, it required more than ten days for normalization. There were no statistically significant differences in the levels of c-AP and LDH activities between patients with and without respiratory complications.

Activity of c-AP and LDH in Patients With Rubella

Because we measured serum enzyme levels only once at the first visit to our hospital in most patients with rubella, and because we found only several patients who were examined sequentially, we have shown the mean values of the serum enzyme levels, divided according to the day after the onset of rash (Table 2). The mean value of c-AP reached the upper limit of the normal range on the day that the rash appeared, and it was 81.6 ± 24.4 U/L, a mildly elevated level, three days after the onset of rash.

The mean value of LDH was normal until one day after the onset of rash, and it reached 674.0 ± 168.8 U/L, a moderately elevated level, four days after the onset of rash. The relative percentages of LDH$_3$ and LDH$_4$ increased, with LDH$_3$ predominating, although LDH$_5$ was normal. The absolute activity of LDH isozymes was the greatest for LDH$_3$ between two days and four days after the onset of rash.

The mean values of AST and ALT were normal on all occasions. The AP and GGT levels were within the normal range in all patients.

COMMENT

As we have reported previously,[1,2] c-AP and LDH activities increased markedly in the 19 patients with measles infection. Cytosol aminopeptidase activity was examined further in this study, and it was shown that in as many as five (26.3%) of the patients, it was over 300 U/L, an unusually high level. Therefore, increased c-AP activity is presumably a common and important finding in measles infection, along with increased LDH.

We have demonstrated that in patients with rubella, increased serum c-AP and LDH activities, with LDH$_3$ predominating, are as commonly seen as in patients with measles. However, values of both enzymes in patients with measles are much higher than those in patients with rubella. Compared with the mean values at three days after the onset of rash in the patients with rubella, c-AP is about threefold higher (269.7 U/L vs 81.6 U/L) and LDH is twofold higher (1149.5 U/L vs 634.8 U/L) in the patients with measles.

Although c-AP and LDH levels peaked almost concurrently in patients with measles and rubella infection, c-AP levels returned to within the normal range more rapidly. Perhaps a shorter half-life of c-AP was reflected in the rapid fall in its concentration in serum.[9]

Concerning the origin of both enzymes in measles infection, we have reported that perhaps, before the appearance of rash, c-AP and LDH levels increase slightly through the direct destruction of lymphocytes by measles virus, and with the appearance of rash, infected lymphocytes are destroyed simultaneously by immunologic reaction, thus causing a massive release of intracellular c-AP and LDH. We have also elucidated that there is almost no possibility of the two enzymes originating from other organs, such as the liver and lung.[1,2]

Rubella virus has been shown to infect human lymphocytes.[18] Because the hemagglutination inhibition antibody becomes detectable with the appearance of rash,[19] the rash is probably a manifestation of an immunologic reaction. In this study, we have shown that c-AP and LDH activities increased with the appearance of rash in the patients with rubella, while those of ALT and LDH$_5$ were normal. Therefore, the increased c-AP and LDH activities in the serum of patients with rubella probably originated from the destruction of infected lymphocytes, as in measles.

In our previous study,[2] we pointed out that when the measles virus infects lymphocytes in vivo, it probably stimulates them to increase intracellular c-AP and LDH, and the infected lymphocytes are eventually destroyed. It was demonstrated that when T-cell mitogens, such as phytohemagglutinin A, were used for lymphocyte activation, a significant increase in intracellular c-AP and LDH activities was observed.[20,21] On the other hand, it was reported that when stimulated by B-cell mitogens, such as pokeweed mitogen, the activity of intracellular c-AP did not increase.[21] Therefore, intracellular enzymes such as c-AP and LDH probably increase only when T lymphocytes are stimulated.

Although suppression of the immune system has been shown to occur in a variety of viral infections, measles virus is known to cause profound and prolonged immunosuppression. To explain this, it was suggested that the measles virus directly infects T lymphocytes[22] and that its receptor exists on T lymphocytes.[23]

The marked difference in activities of the two enzymes between patients with measles and rubella probably reflects their infectivity to lymphocytes, especially T lymphocytes. Increased c-AP and LDH activities in serum are probably observed in other viral diseases that are known to infect lymphocytes, such as human immunodeficiency virus.[7,8]

References

1. Sugaya N, Takeuchi Y, Kanno T: Increased lactate dehydrogenase in serum in measles infection. *Clin Chem* 1987;33:661-663.
2. Sugaya N, Takeuchi Y, Kanno T: Increased cytosol aminopeptidase in serum in measles infection. *Clin Chem* 1988;34:212-213.
3. Wróblewski F, Gregory KF: Lactic dehydrogenase isozymes and their distribution in normal tissues and plasma and in disease states. *Ann NY Acad Sci* 1961;94:912-932.
4. Ringoir S, Plum J: LDH isozymes of human T and B lymphocytes. *Clin Chim Acta* 1975;60:379-383.
5. Blatt J, Spiegel RJ, Papadopoulos NM, et al: Lactate dehydrogenase isoenzymes in normal and malignant human lymphoid cells. *Blood* 1982;60:491-494.
6. Csako G, Magrath IT, Elin RJ: Serum total and isoenzyme lactate dehydrogenase activity in American Burkitt's lymphoma patients. *Am J Clin Pathol* 1982;78:712-717.
7. Silverman B, Rubinstein A: Serum lactate dehydrogenase levels in adults and children with acquired immune deficiency syndrome and AIDS-related complex: Possible indicator of B cell lymphoproliferation and disease activity. *Am J Med* 1985;78:728-736.
8. Rubinstein A, Morecki R, Silverman B, et al: Pulmonary disease in children with acquired immune deficiency syndrome and AIDS-related complex. *J Pediatr* 1986;108:498-503.
9. Kanno T, Maekawa M, Kanda S, et al: Evaluation of cytosolic aminopeptidase in human sera: Evaluation in hepatic disorders. *Am J Clin Pathol* 1984;82:700-705.
10. Kohno H, Kanno T: Properties and activities of aminopeptidases in normal and mitogen-stimulated human lymphocytes. *Biochem J* 1985;226:59-65.
11. Saito M, Takegoshi T, Aoyagi H, et al: Stimulatory effect of bestatin, a new specific inhibitor of aminopeptidases, on the blastogenesis of guinea pig lymphocytes. *Cell Immunol* 1978;40:247-262.
12. Fischer H, Hambsch K, Reinelt S, et al: Die Serumaktivitat der Leuzinaminopeptidase bei lymphotropen Infektionen und malignen Lymphomen. *Z Gesamte Inn Med* 1979;34:392-394.
13. Hayashi M, Tokuhiro H, Kuto F, et al: Leucine amide specific LAP activity in hematological and lymphogenous disorders. *Rinsho Ketsueki* 1983;24:507-516.
14. Sugaya N, Nirasawa M, Takeuchi Y, et al: Hepatitis in acquired rubella infection in children. *AJDC* 1988;142:817-818.
15. Sugiyama M, Tamura S, Hirate F, et al: The method using leucine amide as substrate for the continuous monitoring analysis of leucine aminopeptidase. *Jpn J Clin Chem* 1980;9:313-320.
16. Wróblewski F, LaDue JS: Lactic dehydrogenase activity in blood. *Proc Soc Exp Biol Med* 1955;90:210-213.
17. Henry RJ, Chiamori N, Golub OJ, et al: Revised spectrophotometric methods for the determination of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and lactic dehydrogenase. *Am J Clin Pathol* 1960;34:381-398.
18. Chantler JK, Tingle AJ: Isolation of rubella virus from human lymphocytes after acute natural infection. *J Infect Dis* 1982;145:673-677.
19. Horstmann DM: Rubella, in Evans AS (ed): *Viral Infections of Humans*, ed 2. New York, Plenum Medical Book Co, 1982, pp 519-538.
20. Rogers PA, Brenton DP, Hopkinson DA: Changes in activity and isozyme patterns of glycolytic enzymes during stimulation of normal human lymphocytes with phytohaemagglutinin. *Ann Hum Genet* 1980;43:213-226.
21. Kohno H, Kanno T: Properties and activities of aminopeptidases in normal and mitogen-stimulated human lymphocytes. *Biochem J* 1985;226:59-65.
22. Gallagher MR, Flanagan TD: Replication of measles virus in continuous lymphoid cell lines. *J Immunol* 1976;116:1084-1088.
23. Valdimarsson H, Agnarsdottir G, Lachmann PJ: Measles virus receptor on human T cells. *Nature* 1975;225:554-556.

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ARCHIVES OF INTERNAL MEDICINE

The 'Do Not Resuscitate' Order

Palmi V. Jonsson, MD; Michael McNamee, MD; Edward W. Campion, MD (*Arch Intern Med* 1988;148:2373-2375)

Zinc Status in Children and Young Adults With Sickle Cell Disease

Thomas C. Abshire, MD; Jamie L. English; John H. Githens, MD; K. Michael Hambidge, FRCP(Ed)

• **Previous studies have suggested an association of zinc deficiency and short stature in some children and adults with sickle cell disease (SCD). As a result, zinc supplementation has been recommended for these patients. The mechanism for zinc deficiency in certain patients with SCD is unknown, although renal loss of zinc has been suggested as a contributing factor. The zinc status of 29 subjects with SCD and 18 black controls was studied. No evidence of zinc deficiency in our population with SCD was found when plasma and cellular zinc levels were measured. Likewise, levels of two zinc-dependent enzymes, alkaline phosphatase and δ-aminolevulinic acid dehydratase, were normal in these subjects with SCD. Although adolescent subjects with SCD tended to be shorter than control subjects, there was no correlation between the height-for-age z score and plasma zinc levels ($r = -.31$). It was concluded that zinc deficiency was not present in our population with SCD, and that there was no correlation between plasma zinc levels and the height-for-age z score in growing adolescent patients with SCD. These findings suggested that zinc supplementation may not be necessary in all patients with SCD.**

(*AJDC* 1988;142:1356-1359)

Previous studies have shown the presence of zinc deficiency in adults[1-6] and children[7] with sickle cell disease (SCD), although this has not been a uniform finding.[8-11] Zinc deficiency has been implicated in the pathogenesis of certain sickle cell–related problems, such as short stature,[4,5,12] leg ulcers,[3] impaired neutrophil function,[13] and hypogonadism.[5,14,15] The mechanism for zinc deficiency documented in some patients with SCD is unknown, although several investigators have proposed a relationship to increased losses of this trace mineral via the kidneys.[2,5,7] As a result, zinc supplementation has been recommended for patients with SCD.[2,3,15] Previous studies of zinc status in patients with SCD in Colorado (J.H.G. and K.M.H., unpublished data) did not detect a deficiency in this patient population. In addition, little information has been published on the zinc status of children and teenagers with SCD. Therefore, this study was undertaken to answer the following questions: (1) Does zinc deficiency (as determined by measuring plasma and cellular zinc levels and certain zinc-dependent enzyme levels) occur in children and young adults with SCD? (2) Is urinary zinc excretion increased in these patients with SCD? (3) Does height correlate with zinc status in adolescents with SCD?

SUBJECTS AND METHODS

Twenty-nine black subjects from the Colorado Sickle Cell Treatment and Research Center, Denver, and 18 black controls were studied. All subjects with SCD were confirmed to have a sickle hemoglobinopathy by hemoglobin (Hb) electrophoresis and by hematologic parameters. These 29 subjects were representative of the Colorado sickle cell population in terms of disease severity (mild, 12; moderate, 12; and severe, five), and they were studied sequentially during a 15-month period in the comprehensive sickle cell clinic. Data were analyzed for the entire group of subjects with SCD (19 male and ten female), as well as separately according to the Hb pattern: hemoglobin SS disease (HbSS) (n = 18), hemoglobin SC disease (HbSC) (n = 6), and sickle β^+ thalessemia (HbS-β^+) (n = 5). No subject had evidence of chronic end-organ damage (heart, lung, or kidney) and were in a steady state of health at the time of the study. Likewise, no subjects had experienced a recent infection or painful crisis within two weeks of being studied, or were transfused within the last three months. The mean age of subjects with SCD was 16.8 ± 10.2 (± SD) years, with a range of 22 months to 44 years. Eighteen healthy black subjects (ten male and eight female), with an age range of 7 to 54 years (mean ± SD, 17.8 ± 12.4 years), served as controls. Three of the control subjects had a sickle cell trait. The rest had no evidence of hemoglobinopathy.

Morning blood specimens were obtained from each subject for plasma zinc determination. These specimens were collected in a fasting state from all control subjects and from most (23/29) of the subjects with SCD (one subject had not been fasting before venipuncture, and information on the fasting state of the other five subjects was not known at the time of specimen collection). Care was taken to avoid zinc contamination in the collection and processing of the blood specimens. Blood samples were rejected if visual evidence of hemolysis was noted. The plasma was separated from the red blood cells immediately (less than five minutes), after venipuncture for 15 subjects with SCD and for eight control subjects. The other 14 subjects with SCD had plasma separated from the red blood cells on the average of 44 minutes after specimen collection. Ten control subjects had plasma separation on the average of 51 minutes after venipuncture.

To study the effect of delayed plasma separation on the plasma zinc levels of subjects with SCD, four subjects with HbSS were studied. Blood was drawn and transferred to heparinized tubes, and the plasma was separated at the following time intervals: 0, 30, 60, 120, and 180 minutes. These results were compared with previously established control values that documented the effect of delayed plasma sepa-

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Accepted for publication Aug 24, 1988.

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of Defense of the US government.

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Table 1.—Comparison of Plasma Zn and Urine Zn/Cr Determinations in SCD and Control Subjects*

Group	n	Mean ± SD Age, y	Plasma Zn Level, μmol/L	Urine Zn/Cr Level
Control	18	17.8 ± 12.4	12.2 ± 1.7	0.056 ± 0.032
SCD	29	16.2 ± 10.2	11.6 ± 1.4†	0.062 ± 0.034‡
HbSS	18	15.7 ± 9.2	11.9 ± 1.1§	0.070 ± 0.036‖
HbSC	6	16.3 ± 14.8	11.5 ± 1.6	0.044 ± 0.022
HbS-β†	5	17.9 ± 9.3	10.3 ± 2.2	0.056 ± 0.038

*Zn indicates zinc; Cr, creatinine; SCD, sickle cell disease; HbSS, hemoglobin SS disease; HbSC, hemoglobin SC disease; and HbS-β^+, sickle β^+ thalessemia.

†$P = .22$.

‡$P = .56$.

§$P = .43$.

‖$P = .28$.

Table 2.—Cellular Zn Levels in SCD and Control Subjects*

Group	Mean ± SD Level, μg/10¹⁰ Cells Platelet Zn	Mononuclear Cell Zn
Control	2.12 ± 1.00 (n = 6)	56.6 ± 19.1 (n = 14)
SCD	2.97 ± 1.24 (n = 11)†	66.0 ± 14.3 (n = 8)‡

*Zn indicates zinc; SCD, sickle cell disease.

†$P = .17$.

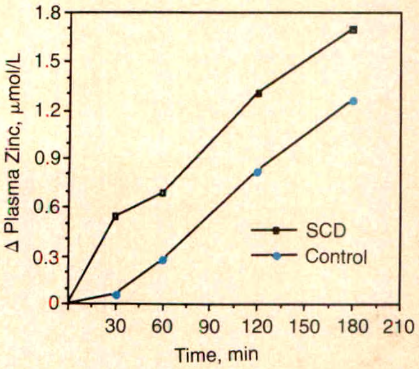
‡$P = .24$.

Table 3.—Comparison of Height, Plasma Zn, and Urine Zn/Cr Determinations in SCD and Control Subjects Aged 9 to 20 Years*

Group	n	Mean ± SD Height-for-Age z Score	Plasma Zn Level, μmol/L	Urine Zn/Cr Level
Control	11	0.24 ± 1.58	11.7 ± 1.5	0.064 ± 0.034
SCD	13	−0.65 ± 1.05†	11.9 ± 1.0	0.064 ± 0.028

*Zn indicates zinc; CR, creatinine; and SCD, sickle cell disease. Correlation for subjects with SCD as follows: plasma Zn level and height ($r = -.31$, $P = .30$); urine Zn/Cr level and height ($r = -.30$, $P = .32$).

†$P = .07$.



Effect that time between sample collection and plasma separation has on plasma zinc levels. For uniformity, both control and sickle cell disease (SCD) plasma zinc levels are recorded as difference (Δ) between each timed zinc level and level found at time 0 minutes.

ration on subsequent plasma zinc levels.[16]

Cellular zinc measurements (platelet and/or mononuclear cell zinc) were assessed in 14 subjects with SCD and in 14 controls. Fifteen milliliters of heparinized blood was centrifuged at 200 g. The platelet-rich plasma was removed, phosphate-buffered saline (PBS) was added, centrifugation was done at 280 g (for five minutes), and the supernatant was discarded. The resulting platelet pellet was resuspended, washed in PBS–ethylene glycol tetra-acetic acid, and centrifuged at 280 g. The platelet pellet was then washed three times in PBS–ethylene glycol tetra-acetic acid, and an aliquot was saved for platelet number assessment and subsequent zinc analysis. Mononuclear cell separation was adapted from the methods of Whitehouse et al[17] and Purcell et al.[18] The cellular layer (red and white blood cells), obtained from the heparinized whole blood sample after platelet removal, was first mixed with acid citrate dextrose solution to restore the blood volume to 30 mL, then inverted, and centrifuged at 280 g for ten minutes. The supernatant was discarded, and PBS was added to a volume of 15 mL, followed by gentle inversion. To this suspension, 30 mL of acid citrate dextrose was added, and the red blood cells were allowed to settle partially. The leukocyte-rich supernatant was removed while it was still pink to avoid excessive loss of the white blood cells in the red blood cell layer. The leukocyte-rich supernatant was centrifuged at 280 g, and the resulting white blood cell pellet was resuspended in PBS. A discontinuous Ficoll-Hypaque gradient was established, with the lower gradient having a specific gravity (SG) of 1.119 and, the upper gradient, an SG of 1.077. The leukocytes were carefully layered over this double gradient and centrifuged at 600 g for 20 minutes. The mononuclear cells were harvested from the PBS/SG 1.119 interface and then subjected to several red blood cell lysing-and-washing steps to eliminate the effect of red blood cell contamination. Aliquots were removed for mononuclear cell count and subsequent zinc determination (micrograms of zinc per 10^{10} cells). Microscopic inspection of a Wright-stained smear confirmed the lack of platelet contamination in the mononuclear cell suspension.

Twenty of the subjects with SCD and 18 controls had serum albumin (Alb), alkaline phosphatase (AP), plasma δ-aminolevulinic acid dehydratase (ALA-D), and somatomedin-C (SM-C) levels determined. Serum Alb is a carrier protein for zinc, and AP and ALA-D are zinc-dependent enzymes. Urine was collected at the time of venipuncture for spot analysis of the zinc/creatinine ratio. The validity of this measurement has been previously documented and was confirmed by control values in this study.[19]

Height was recorded in centimeters for all subjects aged 9 to 20 years, and the height-for-age *z* score (SD of height/age) was calculated. This age range was chosen from data summarized by Serjeant[20] as the age span of greatest falloff in the height of subjects with SCD compared with controls. Informed consent was obtained before participation in the study. All zinc measurements were accomplished by flame atomic absorption spectrophotometry.[16,18,21] Results in Tables 1 through 3 are expressed as mean ± 1 SD. The Student's *t* test and Pearson's correlation were used for statistical analysis. The slopes of each line in the

Figure were compared by the analysis of covariance with random effect.

RESULTS

Table 1 lists the mean levels of plasma zinc and urine zinc/creatinine for both controls and subjects with SCD. The mean plasma zinc levels of subjects with SCD and of subjects with SS alone were not significantly different from corresponding control levels (SCD: $P=.22$; SS: $P=.43$). The mean urinary zinc/creatinine levels for subjects with SCD and SS were also not significantly different from control values (SCD: $P=.56$; SS: $P=.28$).

Cellular zinc levels for subjects with SCD and controls are listed in Table 2. There were no significant differences in platelet ($P=.17$) and mononuclear cell zinc levels ($P=.24$) of subjects with SCD when compared with corresponding control levels.

The serum Alb level was low (36 g/L) in only one subject with HbS-β^+ (plasma zinc level, 8.5 μmol/L), and in one of the control subjects, the serum Alb level was 37 g/L. The serum AP level was just below the lower limit of normal (103 U/L; normal range, 115 to 391 U/L) in one 4-year-old subject with HbSC, and the serum ALA-D level was just below normal (127 U/mL; normal range, 147 to 312 U/mL) in one subject with HbSS. Both of these subjects had normal plasma zinc levels. The serum SM-C level was low for age (0.55 IU/mL; normal range, 0.91 to 3.1 IU/mL) in one subject with HbSS (plasma zinc level, 10.4 μmol/L). The rest of the tested subjects with SCD and the control subjects all had normal levels of Alb, AP, ALA-D, and SM-C.

The height of subjects with SCD, aged 9 to 20 years, was compared with that of controls of the same age range, and then correlated with their respective plasma zinc and urine zinc/creatinine levels. These results are shown in Table 3. The subjects with SCD tended to be shorter than corresponding control subjects ($P=.07$). However, there was no significant correlation between the height-for-age z score and the plasma zinc level ($r=-.31$, $P=.30$), or between the height-for-age z score and the urine zinc/creatinine level ($r=-.30$, $P=.32$).

The effect of plasma separation time on the levels of plasma zinc is depicted in the Figure for four subjects with SS and nine controls. Although the subjects with SS had a greater initial (within 30 minutes) rise in their plasma zinc levels, there was no statistically significant difference between the rate of rise of plasma zinc levels over time when subjects with SS and controls were compared. Furthermore, there was no difference in the mean plasma zinc levels between those subjects with SCD who had immediate and delayed plasma separation ($P=.15$).

COMMENT

Zinc deficiency has been reported in some children with SCD,[7,12,13,22] although the number of studies is small and zinc deficiency was not present in all patients. In only one of these studies,[7] the level of plasma zinc was reported as low. The other three studies documented normal levels of plasma zinc and variable levels of two other determinants of zinc status: red blood cell zinc and carbonic anhydrase (CA). Carpentieri et al[13] utilized CA (a zinc-dependent enzyme) to investigate the zinc status in children with SCD; although they concluded that zinc deficiency occurs in some children with SCD, 40% of these patients had normal levels of CA.

Zinc status in adults with SCD is also variable. Several studies document zinc deficiency in most adults with sickle hemoglobinopathies,[1-6] while other investigators have found normal zinc levels.[8-11] This variation in zinc levels has been explained by geographic differences,[10] or other factors (diet, socioeconomic class),[11] which might modulate disease severity or impact on nutritional status.

Our study of 29 subjects with SCD documented normal mean plasma and cellular zinc levels for a representative sample of the Colorado sickle cell population. Care was taken to collect morning, fasting plasma samples in subjects in a steady state to minimize the effect that circadian rhythm, food, and other factors might have on zinc levels. For the six nonfasting subjects, food intake before blood sampling would be expected to lower plasma zinc levels.[23] However, significantly low plasma zinc levels were not documented in the total or individual groups of subjects with SCD. We did not find a discrepancy between the data obtained from plasma or cellular zinc measurements and that obtained from certain zinc-dependent enzymes, as others have noted.[13] The normal levels of two zinc-dependent enzymes, AP and ALA-D, noted in 19 of 20 subjects with SCD, were consistent with the finding of normal zinc status as determined by measurements of plasma and cellular zinc. We utilized three determinants of zinc status (plasma zinc, cellular zinc, and two zinc-dependent enzymes), because there have been differences of opinion regarding the best method for determining zinc status.[23]

We could not demonstrate a statistically significant difference in the rate of release of zinc over time, from the red blood cells of four subjects with SS when compared with controls (Figure).[16] The group with SS represented in the Figure had a greater initial rise in plasma zinc levels if the red blood cells were separated from plasma at 30 minutes (0.55 μmol/L). However, there was no significant difference between the plasma zinc levels of those subjects with SCD who had immediate (less than five minutes) vs delayed (average, 44 minutes) separation of the red blood cells from plasma.

Our patient group did not demonstrate increased losses of urinary zinc that have been noted in some studies of patients with SCD.[2,5,7] Spot measurement of morning urine zinc/creatinine levels was utilized because of a previously established correlation with 24-hour urine zinc/creatinine excretion[19] and for more accurate urine data collection. The urine zinc/creatinine excretion of our control subjects compared favorably with that of previously established controls.[19] The mechanism of renal handling of zinc is unknown and probably different from other cations.[24] However, some investigators have cited evidence that the mechanism of zinc excretion may be similar to that of sodium excretion (tubular reabsorption),[25] or possibly related to the glomerular filtration rate.[26]

The teenage subjects from the Colorado sickle cell population were shorter than corresponding control subjects, but the difference was not significant ($P=.07$). However, there was no correlation between the height-for-age z score and plasma zinc and urine zinc/creatinine levels. This finding was not surprising, since there are several factors other than zinc status that impact on the height of persons with sickle hemoglobinopathies (eg, chronic anemia, protein intake, and social class).[20] A recent study also found no correlation between serum zinc levels and growth in subjects with SCD.[27] Other studies, however, have reported a causal relationship between zinc status and height,[2,4] although some of these subjects had normal plasma zinc levels.[12] The normal levels of SM-C, noted in 19 of 20 subjects in our study, provide additional support for the lack of correlation between zinc status and height in our population of subjects with SCD. Oner et al[28] observed that the SM-C level was low in zinc-deficient rats with impaired growth, and they concluded that the action of SM-C on skeletal growth was impaired by a deficiency of this trace mineral.

In conclusion, we found no evidence of zinc deficiency in a representative sample of Colorado subjects with SCD and no correlation of plasma zinc or urinary zinc/creatinine levels with height in this population. These results suggest that the Colorado sickle cell population may be different from other groups with SCD. Perhaps other factors, such as diet and socioeconomic class, may explain the geographic differences in zinc status among individuals with sickle hemoglobinopathies. Thus, our findings indicate that zinc supplementation may not be necessary in all patients with SCD.

This study was supported in part by grants RR-69 from the General Clinical Research Centers Program, Division of Research Resources, and 5R22 DK 12432 from the Studies of Human Zinc Deficiency, National Institutes of Health, Bethesda, Md; by the Colorado Sickle Cell Treatment and Research Center, Denver.

The authors wish to thank Peter Lane, MD, for editorial assistance, and Donna Dixon RN, MS, sickle cell center nurse coordinator, and Jacquie O'Connell MLTCASCP, laboratory technician for helpful assistance.

References

1. Karayalcin G, Rosner F, Kim KY, et al: Plasma-zinc in sickle cell-anaemia. *Lancet* 1974;1:217.

2. Prasad AS, Schoomaker EB, Ortega J, et al: Zinc deficiency in sickle cell disease. *Clin Chem* 1975;21:582-587.

3. Serjeant GR, Galloway RE, Gueri MC: Oral zinc sulphate in sickle-cell ulcers. *Lancet* 1970;1:891-893.

4. Prasad AS, Cossack ZT: Zinc supplementation and growth in sickle cell disease. *Ann Intern Med* 1984;100:367-371.

5. Prasad AS, Ortega J, Brewer GJ, et al: Trace elements in sickle cell disease. *JAMA* 1976; 235:2396-2398.

6. Niell HB, Leach BE, Kraus AP: Zinc metabolism in sickle cell anemia. *JAMA* 1979; 242:2686-2687.

7. Karayalcin G, Lanzkowsky P, Kazi AB: Zinc deficiency in children with sickle cell disease. *Am J Pediatr Hematol Oncol* 1979;1:283-284.

8. Butler LC, Taylor ML, McCurdy PR: Zinc and copper investigations in sickle cell anemia, in Kirchgessner M (ed): *Proceedings of the Third International Symposium on Trace Elements: Metabolism in Man and Animals.* Munich, University of Munich, 1978, pp 366-369.

9. Eaton JW, Berger E, White JG, et al: Metabolic and morphologic effects of intraerythrocytic calcium: Implications for the pathogenesis of sickle cell disease, in Brewer GJ, Prasad AS (eds): *Zinc Metabolism: Current Aspects in Health and Disease.* New York, Alan R Liss Inc, 1977, vol 14, pp 275-293.

10. Kapu MM, Fleming AF, Ezem BU: Plasma-zinc in sickle-cell anaemia. *Lancet* 1976;1:920.

11. Alayash AI, Dafallah A, Al-Quorain A, et al: Zinc and copper status in patients with sickle cell anemia. *Acta Haematol* 1987;77:87-89.

12. Daeschner CW, Matustik MC, Carpentieri U, et al: Zinc and growth in patients with sickle cell disease. *J Pediatr* 1981;98:778-780.

13. Carpentieri U, Smith L, Daeschner CW, et al: Neutrophils and zinc in infection-prone children with sickle cell disease. *Pediatrics* 1983;72:88-92.

14. Abbasi AA, Prasad AS, Ortega J, et al: Gonadal function abnormalities in sickle cell anemia: Studies in adult male patients. *Ann Intern Med* 1976;85:601-605.

15. Prasad AS, Abbasi AA, Rabbani P, et al: Effect of zinc supplementation on serum testosterone level in adult male sickle cell anemia subjects. *Am J Hematol* 1981;10:119-127.

16. English JL, Hambidge KM, Goodall MJ: Evaluation of some factors that may affect plasma or serum zinc concentrations, in Hurley L (ed): *Trace Elements in Man and Animals-6.* New York, Plenum Publishing Corp, in press.

17. Whitehouse RC, Prasad AS, Rabbani PI, et al: Zinc in plasma, neutrophils, lymphocytes, and erythrocytes as determined by flameless atomic absorption spectrophotometry. *Clin Chem* 1982;28:475-480.

18. Purcell SK, Hambidge KM, Jacobs MA: Zinc concentration of mononuclear and polymorphonuclear leukocytes. *Clin Chim Acta* 1986;155:179-184.

19. Canfield W, Hambidge KM, Johnson L: Predicting 24 hour zinc excretion using fractional urine collections, abstracted. *Am J Clin Nutr* 1982;35:842.

20. Serjeant GR: Physical and sexual development, in Serjeant GR (ed): *Sickle Cell Disease.* New York, Oxford University Press Inc, 1985, pp 269-280.

21. Hambidge KM, Krebs NF, Sibley L, et al: Acute effects of iron therapy on zinc status during pregnancy. *Obstet Gynecol* 1987;70:593-596.

22. Daeschner CW, Carpentieri U, Goldman S, et al: Zinc deficiency and blood lymphocyte function with sickle cell disease. *Eur J Haematol* 1985;35:186-190.

23. Hambidge KM: Assessing the trace element status of man. *Proc Nutr Soc* 1988;47:37-44.

24. Steele TH: Dissociation of zinc excretion from other cations in man. *J Lab Clin Med* 1973;81:205-213.

25. Watkins DW, Antoniou LD, Shalhoub RJ: Urinary zinc in relation to other cations and flow during volume expansion and intravenous chlorothiazide. *Can J Physiol Pharmacol* 1981; 59:562-566.

26. Lau AL, Failla ML: Urinary excretion of zinc, copper and iron in the steptozotocin-diabetic rat. *J Nutr* 1984;114:224-233.

27. Finan AC, Elmer MA, Sasanow SR, et al: Nutritional factors and growth in children with sickle cell disease. *AJDC* 1988;142:237-240.

28. Oner G, Bhaumick B, Bala RM: Effect of zinc deficiency on serum somatomedin levels and skeletal growth in young rats. *Endocrinol* 1984;114:1860-1863.

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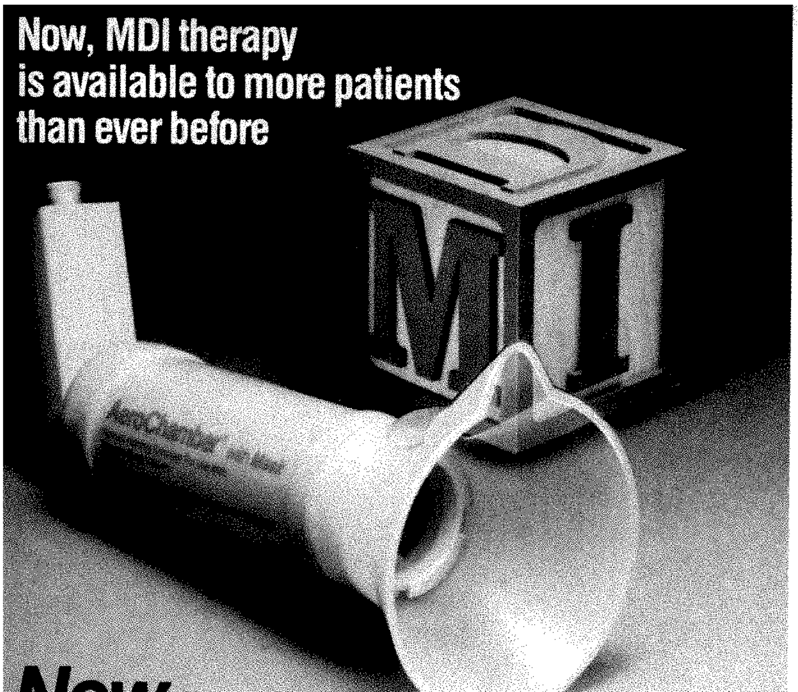

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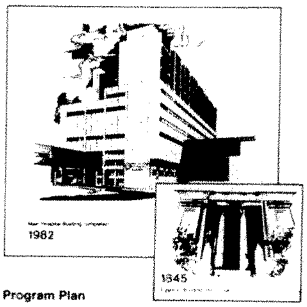

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Sports Medicine

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Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*Exercise and physical fitness have been demonstrated to be beneficial for many physiological and pathologic situations. Now the positive psychological benefits of exercise have been demonstrated for youngsters who have been incarcerated. One of the essential components to improved physical performance is self-discipline. If, in addition to feeling better about themselves, these youths can learn the importance of self-discipline, it would appear that improved physical fitness would be adjunctive therapy in the rehabilitation of this significant segment of our population.*—W.B.S.

Physical and Psychological Effects of Aerobic Exercise in Delinquent Adolescent Males

James R. MacMahon, MD, Ruth T. Gross, MD

• Aerobic exercise has been associated with improved psychological status and physical fitness in adults, but its effects in adolescents have been less clear. This study evaluated the effects of aerobic exercise on the self-concept, depression level, and physical fitness of juvenile delinquents. Ninety-eight incarcerated youths who volunteered to participate were assigned in a blind fashion to one of two exercise programs lasting three months. Sixty-nine completed all phases of the study and are the subjects of this report. One exercise program (32 subjects) emphasized aerobic exercise; the other (37 subjects), limited exertion. Before and after participating, each subject underwent measurement of self-concept, mood, and physical fitness. While the aerobic and comparison groups were initially similar, the data demonstrated an association between participation in the aerobic exercise program and improved self-concept, mood, and fitness. Improvement in psychological variables was not dependent on improved physical fitness and was not related to preintervention measures.

(*AJDC* 1988;142:1361-1366)

Accepted for publication July 18, 1988.
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Aerobic exercise has been associated with improvements in mood,[1-4] social success, and general psychological well-being in adults.[5,6] Although aerobic exercise has been shown to improve physical fitness in various age groups, including adolescents,[7] its psychological effects in this age group are not known. Delinquent adolescents possess a poorer self-image[8,9] and are more depressed[10] than their normal peers. The question thus arose as to whether a relationship can be demonstrated between participation in an aerobic exercise program and improvements in the mood and self-concept of juvenile delinquents. If aerobic exercise offers more psychological benefits than a less physically strenuous program in this population, aerobic exercise might play a role in rehabilitation programs for delinquent adolescents.

Numerous studies have attempted to assess the effects of exercise on cognition, personality, and mood variables. Comprehensive reviews of these studies have demonstrated methodo-

Table 1.—Characteristics of Initial Participants (N = 98)

Characteristic	Subjects
Age, y	
Mean	16.3
Range	14-18.25
Sentence, mo	
Mean	5.75
Range	4-12
Ethnicity, No. (%) of subjects	
White	50 (51)
Hispanic	41 (42)
Black	6 (6)
Asian	1 (1)
Two-parent home, No. (%) of subjects*	18 (19)
Education status, No. (%) of subjects	
Below age expectation†	72 (73)
Special education‡	39 (40)

*Including stepparents.
†No participant was identified as academically advanced.
‡Enrolled in special education program or undergoing individual education planning.

Table 2.—Baseline Measurements and Descriptive Data

Variable and Facility	Subjects Participating Fully (n=69)				Dropouts (n=29)	
	Aerobic Group		Comparison Group			
	Mean ± SD	No. of Subjects	Mean ± SD	No. of Subjects	Mean ± SD	No. of Subjects
Initial self-concept score*						
1	55.9 ± 12	16	51.7 ± 11	23	53.6 ± 13	13
2	53.3 ± 10	16	54.4 ± 10	14	55.8 ± 10	16
1 and 2	54.6 ± 11	32	52.7 ± 11	37	54.6 ± 13	29
Initial Beck Depression Inventory score*						
1	13.6 ± 10	16	16.3 ± 11	23	15.8 ± 11	13
2	17.5 ± 11	16	18.1 ± 11	14	16.7 ± 10	16
1 and 2	15.6 ± 10	32	17.0 ± 11	37	16.3 ± 11	29
Initial physical working capacity†						
1	587.4 ± 87	16	591.3 ± 96	23	601.0 ± 85	13
2	647.8 ± 92	16	672.0 ± 85	14	670.0 ± 92	16
1 and 2	617.6 ± 96	32	621.8 ± 99	37	639.1 ± 88	29
Age, y‡						
1	15.4 ± 0.6	16	15.7 ± 0.5	23	15.6 ± 0.5	13
2	17.1 ± 0.5	16	17.3 ± 0.4	14	17.2 ± 0.7	16
1 and 2	16.4 ± 1.1	32	16.2 ± 0.8	37	16.7 ± 0.9	29
Time of incarceration, mo*						
1	5.5	16	5.6	23	5.6	13
2	5.8	16	6.0	14	5.8	16
1 and 2	5.7	32	5.8	37	5.7	29

*By two-way analysis of variance (group × facility), there was no significant effect of group, facility, or group-facility interaction.

†Kilopond-meters per minute divided by subject's height in meters. By two-way analysis of variance (group × facility), the following values were obtained: aerobic group vs comparison group ($F=0.323$; $df=1,65$; $P=.572$), facility 1 vs facility 2 ($F=9.845$; $df=1,65$; $P<.01$), and group-facility interaction ($F=0.202$; $df=1,65$; $P=.654$).

‡By two-way analysis of variance (group × facility), the following values were obtained: aerobic group vs comparison group ($F=0.069$; $df=1,65$; $P=.794$), facility 1 vs facility 2 ($F=187.0$; $df=1,65$; $P<.001$), and group-facility interaction ($F=3.484$; $df=1,65$; $P<.06$).

logic weaknesses, including voluntary group assignment, comparisons of dissimilar groups, and inadequate documentation of the duration or physical intensity of the exercise.[11-15] It remains unclear whether psychological benefits attributed to exercise are related to the intensity and duration of the exercise, if they are dependent on changes in physical fitness, or whether they are associated with the social and recreational setting in which the exercise programs are carried out.[16] The present study addresses these issues by measuring psychological and physical variables in a prospective comparison of two similarly structured exercise programs of differing physical intensity in a population of incarcerated males 14 to 18 years of age. The study was designed to test the hypothesis that juvenile delinquent males who participate in a structured aerobic exercise program show more improvement in measures of physical fitness, self-concept, and mood than those who participate in a comparable but less vigorous exercise program.

MATERIALS AND METHODS

Subjects

The study population consisted of males 14 to 18 years of age who were incarcerated in the juvenile detention facilities of Santa Clara County, California. Two facilities were involved: facility 1 was for 14- to 16-year-olds and facility 2 was for 16- to 18-year-olds. Youths incarcerated at the facilities when the study began or who arrived over the next two months were invited to participate. Enrollment was limited to those whose incarceration was scheduled to coincide with at least four months of the study, so that each subject would experience three months of an exercise program. By this criterion, 123 youths were eligible. Of these, 98 volunteered and obtained parental consent (52 from facility 1, 46 from facility 2). Characteristics of the 98 are presented in Table 1; data for those who did not volunteer were not available due to issues of confidentiality. Participation in this program was strictly voluntary, and no specific incentives to participate were offered. The study was approved by the Committee for Experimentation on Human Subjects at Stanford University, Palo Alto, Calif.

Design

Once enrolled in the study, the subjects were assigned either to an aerobic exercise program or to a less vigorous comparison exercise program, both of which were incorporated into the usual physical education curriculum. At each facility, youths arriving for incarceration were assigned to one of two curricular schedules corresponding to the two exercise programs to fill vacancies left by those being released from custody. Group assignment was thus carried out by administrative personnel who were unaware of the differences between the assignments. At all stages of this study, the composition of the aerobic group and the comparison group was similar with regard to baseline levels of the outcome measures obtained for the purpose

Table 3.—Changes in Outcome Variables

Variable and Facility	Aerobic Group		Comparison Group	
	Mean ± SD	No. of Subjects	Mean ± SD	No. of Subjects
Self-concept score*				
1	6.38 ± 6.5	16	2.48 ± 7.0	23
2	4.50 ± 5.7	16	1.64 ± 9.5	14
1 and 2	5.44 ± 6.1	32	2.16 ± 8.9	37
Beck Depression Inventory score†				
1	−3.38 ± 6.0	16	−0.7 ± 6.8	23
2	−6.19 ± 7.2	16	0.21 ± 7.8	14
1 and 2	−4.78 ± 6.9	32	−0.35 ± 7.6	37
Physical working capacity‡				
1	67.48 ± 44	16	17.20 ± 53	23
2	78.63 ± 78	16	28.69 ± 59	14
1 and 2	73.05 ± 62	32	21.55 ± 55	37

*By two-way analysis of variance (group × facility), the following values were obtained: aerobic group vs comparison group ($F = 3.827$; $df = 1,65$; $P = .055$), facility 1 vs facility 2 ($F = 0.569$; $df = 1,65$; $P = .453$), and group-facility interaction ($F = 0.086$; $df = 1,65$; $P = .770$).

†By two-way analysis of variance (group × facility), the following values were obtained: aerobic group vs comparison group ($F = 5.826$; $df = 1,65$; $P = .019$), facility 1 vs facility 2 ($F = 0.235$; $df = 1,65$; $P = .630$), and group-facility interaction ($F = 1.065$; $df = 1,65$; $P = .306$).

‡Kilopond-meters per minute divided by subject's height in meters. By two-way analysis of variance (group × facility), the following values were obtained: aerobic group vs comparison group ($F = 12.107$; $df = 1,65$; $P = .001$), facility 1 vs facility 2 ($F = 0.611$; $df = 1,65$; $P = .437$), and group-facility interaction ($F = 0$; $df = 1,65$; $P = .991$).

Table 4.—Distribution of Baseline Beck Depression Inventory Scores (N = 69)

Beck Depression Inventory Score	No. (%) of Subjects	Clinical Interpretation
0-9	19 (27)	Not depressed
10-19	27 (41)	Mild to mild-moderate depression
20-29	14 (20)	Moderate-severe depression
≥30	9 (12)	Severe depression

of this study and their sociodemographic characteristics, including age and time of incarceration (Table 2).

At each detention facility, the boys assigned to the aerobic program experienced 40 minutes of sustained exercise three days per week. Their program included long-distance running and vigorous basketball, causing a sustained elevation of each subject's heart rate to above 160 beats per minute, a level reported to have a training effect.[7] The comparison exercise program for each facility was similar in duration and frequency and was coached by the same personnel as the aerobic program, but it consisted of activities designed to avoid sustained elevation of heart rates. This program included baseball, volleyball, basketball foul-shot contests, and instruction in wrestling. The exercise programs were administered by the physical education staff of the ranches, all of whom have training and experience in youth sports programs. These instructors were aware of the intended difference in the physical intensity of the exercise programs, but they were unaware of the psychological assessments. The intensity of each exercise program was monitored weekly by having two subjects in each group, chosen at random, wear a portable heart rate monitor (Exersentry, Respironics Inc, Monroeville, Pa) during the exercise period. These monitors have alarms, which for this study were set for pulse rates below 160 beats per minute in the aerobic group or above 120 beats per minute in the comparison group. At no time did an alarm sound for more than 20 s. The intended function of the heart rate monitors was to measure and confirm the difference in intensity between the two exercise programs. Although the instructors were unable to detect subjectively a difference between monitored days and unmonitored days, the impact of the alarms on the exercise programs cannot be discounted. Measurements of self-concept, mood, physical fitness, and anthropometry for each subject were recorded by one of the authors (J.R.M.) before and immediately after three months of participation in one of the exercise programs.

Instruments

The instruments for measuring the outcome variables were selected because of their widespread acceptance and usage in this age group, their standardization, and their feasibility of administration.

The self-concept of each youth was evaluated by use of the Piers-Harris Children's Self-Concept Scale.[17] The 80 items of this questionnaire measure the individual's general self-concept and require a simple yes/no answer.

Mood was measured using the Beck Depression Inventory (BDI).[18] Though it was originally designed as an adult measure of depression,[19] normative data have been provided for the use of this instrument in an adolescent population.[20] The BDI contains 21 items that assess the cognitive, behavioral, affective, and somatic components of depression. Higher scores represent more severe depression, and guidelines have been suggested to classify varying degrees of depression.[21] The measurements of self-concept and mood were completed by each subject in writing at an individual desk, with an examiner present to explain the questionnaires and to help with reading difficulties.

Cardiovascular physical fitness was assessed by submaximal exercise testing using a cycle ergometer (Schwinn Inc, Chicago) with an electrically calibrated workload. The workload that raised the subject's heart rate to 170 beats per minute, known as the physical working capacity (PWC-170) of that individual, was used as a measure of physical fitness. This value has been shown to correlate with measures of maximal oxygen consumption.[22] Following the protocol of Wahlund,[23] the PWC-170 was calculated for each subject by extrapolation, using the heart rate plateaus recorded when the subject pedaled at each of three standard workloads. Also recorded for each subject were his age, height, and weight (by balance scale). The PWC-170 values, in kilopond-meters per minute, were corrected for body size using the subject's height in meters.[24] The corrected PWC-170 values will be referred to as *PWC* henceforth.

Statistical Methods

Data were analyzed using a 2 × 2 analysis of variance (ANOVA) (exercise program × facility) on baseline measures and on pre-post changes in the outcome variables. This corresponds to the results of a repeated-measures ANOVA and assesses the effect of the exercise program, the facility, and their possible two-way inter-

Table 5.—Relationships Among Baseline Measures and Changes in Outcome Variables After Participation in Exercise Program ($N=69$)*

	r by Baseline Measure or Change in Outcome Variable						
Baseline Measure or Change in Outcome Variable	Baseline Self-Concept Score	Baseline Beck Depression Inventory Score	Baseline Physical Working Capacity	Age, y	Change in Self-Concept Score	Change in Beck Depression Inventory Score	Change in Physical Working Capacity
Baseline self-concept score	1	...	...	...	...	...	...
Baseline Beck Depression Inventory score	−.33†	1	...	...	...	...	...
Baseline physical working capacity	.06	−.15	1	...	...	...	...
Age, y	−.18	.20	.29‡	1	...	...	...
Change in self-concept score	−.20	−.22	.08	−.04	1	...	...
Change in Beck Depression Inventory score	.07	−.14	.10	−.06	−.02	1	...
Change in physical working capacity	−.13	.15	.11	.21	.08	−.10	1

*Pearson correlation coefficient matrix.
†$P<.01$.
‡$P<.05$.

action on the dependent variables. To compare subjects who completed the study with those who left, the Student's t test was used. A matrix of Pearson correlation coefficients was employed in assessing the relationships among selected baseline measures, including the three variables being studied. As an exercise in exploratory data analysis, a correlation matrix was used also to identify possible correlations among the changes that occurred in self-concept, mood, and physical fitness over the course of the study. Statistical significance was defined as $P<.05$.

RESULTS

Of 98 subjects initially enrolled, 45 were assigned to the aerobic program and 53 to the comparison program. Sixty-nine (70%) completed the study: 32 (71%) in the aerobic program and 37 (70%) in the comparison group. Failure to complete the study resulted from subjects being released earlier than originally scheduled (seven in the aerobic group, nine in the comparison group), being transferred to other facilities (one in the aerobic group, one in the comparison group), running away (one in the aerobic group, one in the comparison group), or withdrawing voluntarily (four in the aerobic group, five in the comparison group). The four subjects who were transferred to other facilities or who escaped were all in the facility for younger boys; those who were released early or withdrew voluntarily came from both facilities. A review of the initial measurements and subject ages revealed no characteristics differentiating the 69 who completed the study from those who departed (Table 2).

A two-factor ANOVA (exercise program × facility) was used to examine the baseline data for the subjects who completed the study (Table 2). There were no significant effects of group assignment on any of the independent variables, including self-concept, depression level, physical fitness, age, and time of incarceration. There were significant differences ($P<.01$) between subjects in the two facilities with regard to age and baseline measures of physical fitness. No significant two-way interaction of exercise program and facility was identified.

Measurements carried out immediately after three months of participation in the exercise program demonstrated significantly greater improvement in mood ($P<.05$) and physical fitness ($P<.001$) among subjects who participated in the aerobic exercise progams. Improvement in self-concept scores was also greater for the aerobic group members, but at $P=.055$ (Table 3). Two-factor (2×2) ANOVA of the pre-post changes in measurements revealed no significant effect of the facility at which the exercise program occurred and no two-way interaction of the facility and exercise program (Table 3).

Using the standardized scoring provided with the Piers-Harris Children's Self-Concept Scale, the mean (±SD) baseline score of all 69 subjects (53.4 [±11]) was in the 51st percentile. The aerobic subjects' mean score increased from 54.6 (±11) to 60 (±12), an increase from the 55th to the 69th percentile. The comparison subjects' mean scores (preintervention, 52.7 [±10]; postintervention, 54.9 [±11]) increased only from the 49th to the 55th percentile.

For the baseline BDI, the mean score for all 69 subjects was 16.4 (±10); the median score was 14. The distribution of BDI scores and clinical implications based on standard guidelines used in interpreting this scale are displayed in Table 4 and demonstrate that only 27% of the subjects were categorized as *not depressed*.[21] The mean BDI scores before intervention were 15.6 (±10) and 17.3 (±11) for the aerobic and comparison groups, respectively (Table 2). After participation, the aerobic and comparison groups experienced a mean decrease in BDI scores of 4.78 (±6.9) and 0.35 (±7.6), respectively (Table 3), indicating an improvement in mood among the aerobic subjects.

In measures of physical fitness, the subjects of this study had values within the range previously reported for normal adolescents.[24] The mean increase in PWC for subjects assigned to an aerobic exercise program was 73 U compared with 21 U for the comparison subjects; the effect of the exercise program was significant ($P<.001$) (Table 3).

A matrix of Pearson product-moment correlation coefficients (Table 5) revealed a negative correlation of .33

($P<.01$) between the baseline measures of depression and self-concept and a correlation of .29 ($P<.05$) between a subject's age and his baseline physical fitness. The measured *changes* in self-concept, depression, and physical fitness were not correlated and were independent of the subject's age and baseline measures.

COMMENT

This is, to our knowledge, the first study of the psychological and physical changes associated with aerobic exercise using a prospective comparison of two exercise programs for delinquent adolescents. Whether the findings of this study can be generalized to other groups of juvenile delinquents remains to be tested.

The major finding of this study is that aerobic exercise was associated with greater improvement in measures of self-concept, depression, and fitness than was participation in less vigorous activity, with depression and fitness reaching statistical significance. Though one study cannot with certainty address the issue of whether exercise must be aerobic to be of benefit, these data suggest that aerobic exercise has more psychological benefit than less vigorous activity. However, the data presented in the correlation matrix imply that the psychological impact of aerobic exercise is independent of its effect on cardiovascular physical fitness.

Previous investigations have suggested that psychological benefits attributed to exercise may in fact be related to the social reinforcement and recreational distraction associated with the exercise programs[5,25] or could be caused by a sense of achievement or increased control or mastery of body function.[26] Others have suggested that changes in circulation or levels of endorphins, norepinephrine, or other amine neurotransmitters are involved.[11,27-32] By using an incarcerated population that eats, sleeps, studies, and plays in a strictly supervised environment of coercive conformity, the design of this study controls for such relevant issues as extracurricular activities, external social reinforcement, drug habits, and other variations in environment and curriculum. The findings of this study are reinforced by the inclusion of the comparative exercise program, which was similar to the aerobic program in structure and administration. In addition, the documentation of the intensity of the exercise was a critical component of the design. The measures of physical fitness serve two functions; besides demonstrating that aerobic exercise affects cardiovascular fitness among adolescents, they ensure that the exercise programs differed sufficiently in intensity to have measurably different physical effects. It should be noted that several potentially relevant factors could not be controlled for in this study: school performance, counseling provided by the detention facilities, individual reaction to a restrictive and somewhat punitive environment, the impact of separation from family, and relationships such as gang membership. Future studies will need to address the process through which aerobic exercise influences self-concept and mood and will need to determine whether it confers benefits in other areas, such as academic performance or social skills.

Future studies might also be directed at identifying subjects for whom aerobic exercise may be particularly beneficial. Results of earlier studies suggest that those who are more severely afflicted with psychological impairments or who are considered physically unfit may show greater response to exercise than those considered normal in these respects.[33] Data from this study, however, do not show correlations between initial self-concept or mood and response to aerobic exercise, nor are we able to estimate the duration of an exercise program to maximize psychological benefits.[34]

Although the delinquent adolescents participating in this study had a mean self-concept score in the 51st percentile and a mean depression score in the mildly depressed range, it is unclear how representative these findings are of delinquent male adolescents in general. Studies of other juvenile delinquents[35-37] have reported conflicting results in these measures. Certainly, the voluntary nature of participation and the absence of inducements to complete this study may have allowed a systematic bias to occur in the initial enrollment as well as in the decision to drop out. Although those who declined to enroll were reported to be similar to enrollees with regard to race and time of incarceration, no information about their mood, self-concept, or physical fitness was available. The high scores on the BDI are certainly of concern, as they suggest a high prevalence of depression among a group of incarcerated youths willing to participate voluntarily in a study such as this.

The design of this investigation was influenced by the institutional environment in which it was carried out. Detention facilities admit and release youths intermittently, unlike regular schools, and enrollment therefore occurred over a period of two months. The process of group assignment, described earlier, resulted at each facility in an aerobic group of subjects and a comparison group that at all times during the study were similar in age, time of incarceration, and baseline measurements of the physical and psychological variables included in this study. Admittedly, this process of group assignment was not strictly random. Nevertheless, the similarities of the two groups at each facility and their sharing of living quarters, meal times, and extracurricular activities may have served to randomize the error effects or to control for those factors, such as self-selection of groups or dissimilarities of groups or programs, that have weakened previous studies. As the regular curricular program included 40 minutes of sports every second day prior to this study, instituting an aerobic exercise program did not interfere with a curriculum already in place. Before this study, the exercise programs in place were similar to the "comparison program" and served as recreation and a time to learn rules of social interaction. One perceived weakness in the design of this study was the inability to have the author (J.R.M.) who recorded measurements of self-concept, mood, and physical fitness be completely unaware of the subjects' group assignment. However, efforts were made to minimize the possible influence of this factor on data collection by mixing groups on days of measurement, gathering written questionnaires in random order, and using identification numbers instead of personal names whenever possible.

Although the specific crime committed or aberrant behavior that led to each subject's incarceration was not recorded during this study, the time of scheduled incarceration was used as a measure of group similarity. A majority of the youths incarcerated in these facilities were convicted of crimes that in adult courts would be felonies (eg, sale of drugs, assault, robbery), although some were there for serious misdemeanors (eg, vandalism, petty theft). Voluntary participation in a study is recognizably different from obligatory attendance at an exercise class, and this difference might have an impact on the psychological outcome of an aerobic exercise program instituted as a truly routine physical education curriculum in a detention facility. This issue was not addressed directly in this study, nor was this study intended to evaluate strategies for implementing aerobic exercise programs in detention facilities or for enhancing youths' participation in such programs.

By involving two separate but similar detention facilities, this study was able to represent a broader age group and to include a greater number of subjects than would otherwise have been available. Comparison of data from the two facilities identified no differences except those related to the age of the subjects. Because the main purpose of the study was to compare aerobic with less vigorous exercise, the results and their interpretation focused on this aspect. The two-factor analysis of variance was used to address some of the issues raised by employing two separate detention facilities, and it permitted testing for significant interaction between the exercise programs and the two facilities.

The results of this investigation support the hypothesis that participation in an aerobic exercise program is associated with measured improvements in self-concept, level of depression, and physical fitness in delinquent male adolescents. Although baseline measures of self-concept and mood as assessed by the Piers-Harris Children's Self-Concept Scale and the BDI were correlated, *improvements* in these two variables were not correlated and occurred independently of changes in physical fitness. If future studies replicate these results, the inclusion of aerobic exercise in remediation programs for delinquent youths should be considered.

This study was supported in part by the General Pediatrics Academic Development Program of the Robert Wood Johnson Foundation, Princeton, NJ.

We thank Helena Kraemer, PhD, for advice and assistance in the statistical interpretation of the data.

References

1. Goldwater BC, Collis ML: Psychologic effects of cardiovascular conditioning: A controlled experiment. *Psychosom Med* 1985;47:174-181.
2. Folkins CH, Lynch S, Gardner MM: Psychological fitness as a function of physical fitness. *Arch Phys Med Rehabil* 1972;53:503-508.
3. Greist JH, Klein MH, Eischens RR, et al: Running as treatment for depression. *Compr Psychiatry* 1979;20:41-53.
4. Morgan WP, Roberts JA, Brand FR, et al: Psychological effects of chronic physical activity. *Med Sci Sports Exerc* 1980;2:213-217.
5. Morgan WP: Affective beneficence of vigorous physical activity. *Med Sci Sport Exerc* 1985; 17:94-100.
6. Morgan WP: *Coping With Mental Stress: The Potential and Limits of Exercise Intervention.* Bethesda, Md, National Institute of Mental Health, 1984, pp 11-14.
7. Bar-Or O: *Pediatric Sports Medicine for the Practitioner.* New York, Springer-Verlag NY Inc, 1983, pp 44-75.
8. Offer D, Ostrov E, Howard KL: *The Adolescent: A Psychological Self Portrait.* New York, Basic Books Inc Publishers, 1981.
9. Kaplan HB: *Deviant Behavior in Defense of Self.* Orlando, Fla, Academic Press Inc, 1980.
10. Cole E, Kumchy CIG: The CIP battery: Identification of depression in a juvenile delinquent population. *J Clin Psychol* 1981;37:880-884.
11. Folkins CH, Sime WE: Physical fitness training and mental health. *Am Psychol* 1981; 36:373-389.
12. Greist JH, Klein MH, Eischens RR, et al: Running through your mind, in Sacks MH, Sacks ML (eds): *Psychology of Running.* Champaign, Ill, Human Kinetics, 1981, pp 5-26.
13. Layman EM: Psychological effects of physical activity, in Wilmor JH (ed): *Exercise and Sport Sciences Reviews.* Orlando, Fla, Academic Press Inc, 1974, vol 2, pp 33-40.
14. Morgan WP: Exercise and mental disorders, in Ryan AJ, Allman FL Jr (eds): *Sports Medicine.* Orlando, Fla, Academic Press Inc, 1974, pp 671-679.
15. Tomporowski PD, Ellis NR: Effects of exercise on cognitive processes: A review. *Psychol Bull* 1986;99:338-346.
16. Phelps JR: Physical activity and health maintenance: Exactly what is known? *West J Med* 1987;146:200-206.
17. Piers EV, Harris DB: *The Piers-Harris Children's Self-Concept Scale.* Los Angeles, Western Psychological Service, 1984.
18. Beck AT, Beamesderfer A: Assessment of depression: The Depression Inventory, in Pichot P (ed): *Psychological Measurements in Psychopharmacology, Modern Problems in Psychometry.* New York, S Karger AG, 1974, vol 7, pp 151-169.
19. Beck AT, Wart CH, Mendelsohn M, et al: An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571.
20. Teri L: The use of the Beck Depression Inventory with adolescents. *J Abnorm Child Psychol* 1982;10:277-284.
21. Beck AT: Measurement of depression: The depression inventory, in *Depression: Causes and Treatment.* Philadelphia, University of Pennsylvania Press, 1970, pp 186-206.
22. DuRant RH, Dover EV, Alpert BS: An evaluation of five indices of physical working capacity in children. *Med Sci Sports Exerc* 1983; 15:83-87.
23. Wahlund H: Determination of the physical working capacity. *Acta Med Scand* 1948; 215(suppl):1-78.
24. Adams FH, Linde LM, Miyake H: The physical working capacity of normal school children. *Pediatrics* 1961;28:55-64.
25. Dishman RK: Medical psychology in exercise and sport. *Med Clin North Am* 1985;69:123-143.
26. Hughes JR: Psychological effects of habitual aerobic exercise: A critical review. *Prev Med* 1984;13:66-78.
27. Ransford CP: A role for amines in the antidepressant effect of exercise: A review. *Med Sci Sports Exerc* 1982;14:1-10.
28. Stein L, Belluzzi JD: Brain endorphin and the sense of well being: A psychobiological hypothesis. *Adv Biochem Psychopharmacol* 1978; 18:299-311.
29. Hollandsworth JG Jr: Some thoughts on distance running as training in biofeedback. *J Sports Behav* 1979;2:71-82.
30. Ismail AH, Trachtman LE: Jogging the imagination. *Psychol Today,* March 1973, pp 79-82.
31. Solomon EG, Bumpus AK: The running meditation response: An adjunct to psychotherapy. *Am J Psychother* 1978;32:583-592.
32. Leonardson GR, Gargiulo RM: Self perception and physical fitness. *Percept Mot Skills* 1978;46:338-340.
33. Weingarten G: Mental performance during physical exertion: The benefit of being physically fit. *Int J Sports Psychol* 1973;4:16-26.
34. Haskell W: Physical activity and health: Need to define the required stimulus. *Am J Cardiol* 1985;55:4d-10d.
35. Calhoun C Jr, Connley S, Bolton JA: Comparison of delinquents and non-delinquents in ethnicity, ordinal position, and self-perception. *J Clin Psychol* 1984;40:323-328.
36. Campbell A: Intrapersonal and interpersonal discrepancy among delinquent and nondelinquent girls: A research note. *J Child Psychol Psychiatry* 1988;29:73-78.
37. Kandel DB, Davies M: Epidemiology of depressive mood in adolescents. *Arch Gen Psychiatry* 1982;39:1205-1212.

Radiological Case of the Month

Jacob Zeiss, MD; Nathaniel D. Wycliffe, MD; Bernard J. Cullen, MD;
Steven Conover, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)

An 8-year-old boy with a history of severe mental retardation, cerebral palsy, and seizure disorder was brought to the emergency room because of a lump in the anterior aspect of upper right side of the chest. His mother denied any history of trauma, other than a fall from a wheelchair while he was on the school bus. Initial roentgenograms showed a healing fracture of the right clavicle (Fig 1). A healing fracture involving the right distal shaft of the ulna was noted by radiographic long-bone skeletal survey (Fig 2). No history of trauma explained the ulnar fracture. Child abuse was suspected, and the child was admitted to the hospital.

Significant history included a normal birth and neonatal period. At 6 weeks of age the patient was the victim of a house fire and received severe burns. Secondary to anoxia he developed seizures, cerebral palsy, and developmental delay. At the time of admission he was functioning at the level of a 6-month-old infant. He was cared for by his mother. Current medications included phenobarbital (30 mg twice daily) and carbamazepine (Tegretol) (100 mg three times a day).

Figure 1.

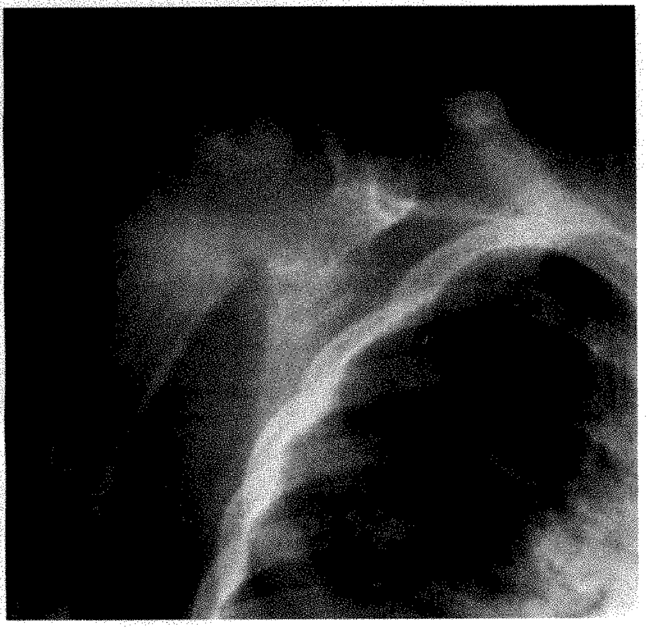
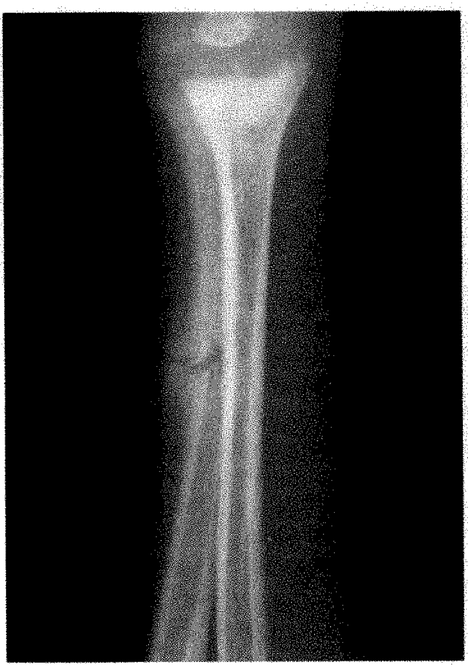


Figure 2.



The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Accepted for publication March 11, 1988.
Contributed from the Departments of Radiology (Drs Zeiss, Wycliffe, and Conover) and Pediatrics (Dr Cullen), Medical College of Ohio at Toledo.
Reprint requests to the Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Denouement and Discussion

Simulated Child Abuse in Drug-Induced Rickets

Fig 1.—Note acutely fractured clavicle and diffuse bone demineralization, with coarse trabecular and cortical thinning of proximal humeral metaphysis. Changes are characteristic of rickets.

Fig 2.—Ulnar fracture is subacute, with callus deposition. Rachitic changes are again noted with particularly characteristic appearance to distal radial metaphysis.

Fig 3.—Left, Rickets is characterized by diffuse osteopenia, cortical thinning (periosteal reaction is found in healing phase of accompanying fractures), trabecular coarsening, widening of epiphyseal growth plate with long bone metaphyses being broadened, cupped, and indistinct. Right, Child abuse is characterized by submetaphyseal fractures of bucket-handle configuration or with fragmentation. If healing, periosteal reaction is present.

Long-term administration of anticonvulsant therapy is associated with rickets and is reported among institutionalized and ambulatory children with seizure disorders.[1-5]

Both phenobarbital and phenytoin sodium (Dilantin) have been incriminated with alteration in vitamin D metabolism. Barbiturates increase catabolism and excretion of vitamin D and its biologically active metabolites by simulating hepatic enzyme activity.[6] A similar mechanism is possible for other anticonvulsant drugs.[7]

Studies have indicated that approximately 35% of children receiving long-term anticonvulsant therapy show abnormally elevated serum alkaline phosphatase levels[5] and 25% show skeletal changes of rickets.[1] The typical roentgenographic features of rickets are shown in Figs 1 and 2. Lack of mineralization at the zone of provisional calcification results in apparent widening of the epiphyseal plate with metaphyseal broadening, fraying, and cupping (Fig 3). Pseudofractures and actual fractures result from diminished bone strength. Periosteal new bone is seen in the healing phase. True fractures occur more frequently in anticonvulsant agent–induced rickets since seizure activity increases the incidence of bony injury.[8] Paterson[9] reports a case of a child with undiagnosed vitamin D deficiency who presented with multiple fractures. Child abuse was suspected until it was ascertained that the roentgenographic abnormalities were features of rickets.

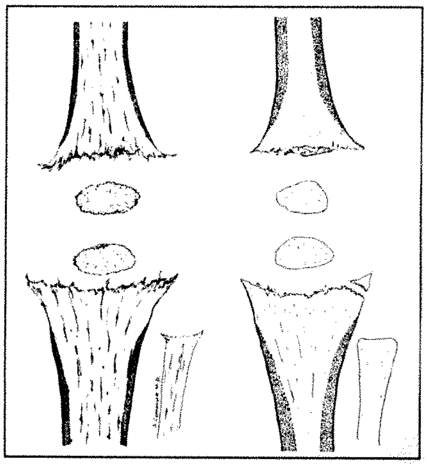
These rachitic changes may be subtle and overshadowed by unexplained fractures. They occur in retarded, epileptic patients who are subject to trauma but who are poor historians, creating a mistaken diagnosis of abuse.

The special child is at greater risk for abuse[10] and has a particular vulnerability to nonaccidental injury or nutritional neglect. Jaudes and Diamond[11] showed that 14% of the children in their study with cerebral palsy were abused. These risk factors need to be taken into consideration when approaching the workup of the handicapped child suspected of nonaccidental injury.

Underlying rickets complicates the radiological diagnosis of abuse. A characteristic skeletal change of battered-child syndrome is submetaphyseal fractures. Abuse fractures of the metaphysis appear as corner fractures, crescent-shaped fractures, or diffuse fragmentation and irregularity of the provisional zone of calcification (Fig 3).

Key differential features include the lack of bone demineralization in abuse (barring coexisting nutritional neglect) and the sharply delineated metaphyseal fractures or fragmentation of abuse vs the irregular, ill-defined fraying of rickets. Differentiation of uncomplicated rickets from characteristic child abuse is quite distinct. However, superimposition of one on the other requires supportive studies.

Figure 3.



Following comprehensive evaluation of this patient and his family, the fractures were considered to be secondary to rickets and related to prolonged anticonvulsant therapy. The patient responded readily to vitamin D administration. Prophylaxis against drug-induced rickets with daily vitamin D supplementation is strongly recommended.[5]

References

1. Tolman KG, Jubiz W, Sannella JJ, et al: Osteomalacia associated with anticonvulsant drug therapy in mentally retarded children. *Pediatrics* 1975;56:45-51.
2. Chan JCM, Kodroff MB, Landwehr DM: Effects of 1,25-dihydroxyvitamin-D_3 on renal function, mineral balance and growth in children with severe chronic renal failure. *Pediatrics* 1981;68:559-571.
3. Morijiri Y, Sato T: Factors causing rickets in institutionalized handicapped children on anticonvulsant therapy. *Arch Dis Child* 1981;56:446-449.
4. Crosley CJ, Chee C, Berman PH: Rickets associated with long-term anticonvulsant therapy in a pediatric out-patient population. *Pediatrics* 1975;56:52-57.
5. Hunt PA, Wu-Chen ML, Handal NJ, et al: Bone disease induced by anticonvulsant therapy and treatment with calcitriol (1,25-dihydroxyvitamin D_3). *AJDC* 1986;140:715-718.
6. Hahn TJ, Birge SI, Scharp CR, et al: Phenobarbital induced alterations in vitamin D metabolism. *J Clin Invest* 1972;51:741-748.
7. Hahn TJ, Shires R, Halstead LR: Serum dihydroxyvitamin D metabolite concentrations in patients on chronic doses of vitamin D_2. *Metab Bone Dis Relat Res* 1983;5:1-6.
8. Moskowitz H, Milikow E: Case report 285. Diagnosis: Osteomalacia (rickets) and cerebellar atrophy secondary to the effects of diphenylhydantoin (dilantin). *Skeletal Radiol* 1984;12:281-283.
9. Paterson CR: Vitamin D deficiency rickets simulating child abuse. *J Pediatr Orthop* 1981;1:423-425.
10. Soeffing M: Abused children are exceptional children. *Except Child* 42:126-133, 1975.
11. Jaudes PK, Diamond LJ: The handicapped child and child abuse. *Child Abuse Negl* 1985;9:341-347.

Picture of the Month

Sami B. Elhassani, MD (*Contributor*);
Murray Feingold, MD (*Section Editor*)

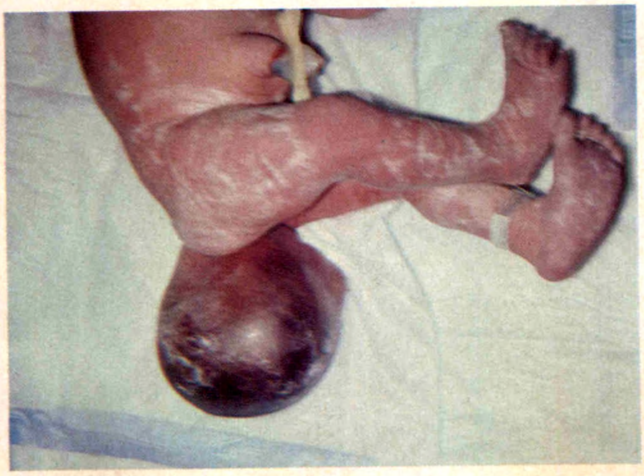


Figure 1.

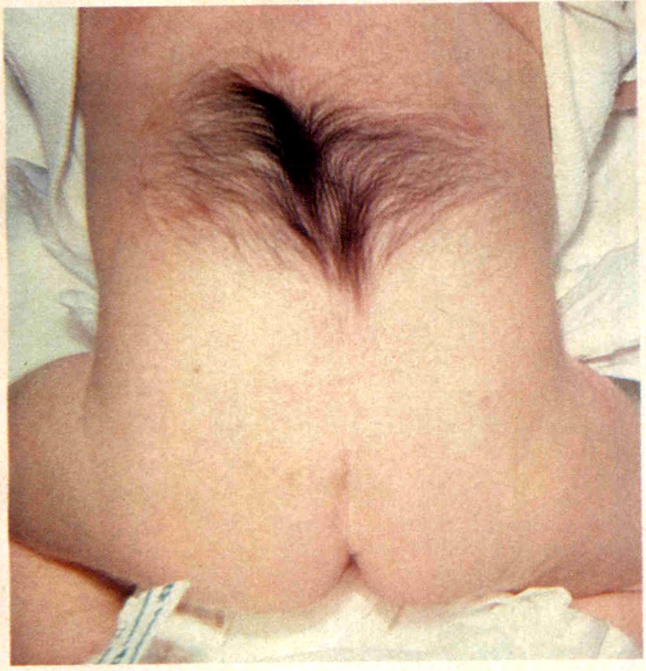


Figure 2.

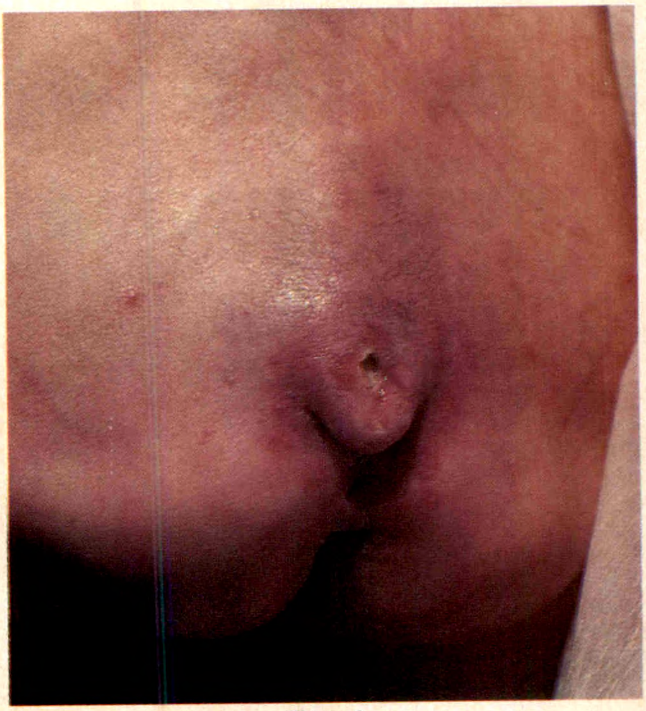


Figure 3.

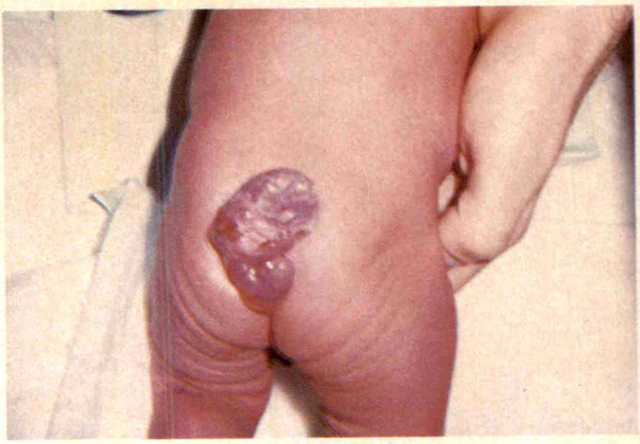


Figure 4.

The statements listed below are best associated with which of the above figure(s):

(*a*) Tethering of the spinal cord may lead to progressive neurologic deficit of the lower limbs.

(*b*) Patients with this type of lesion usually have a normal spinal column and canal.

(*c*) This lesion should be considered in patients who have recurring meningitis.

(*d*) This is a very common skin lesion but is of concern when present in this location.

Accepted for publication May 12, 1988.
Contributed from the Medical University of South Carolina, Charleston.
Reprint requests to National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Sacrococcygeal teratoma.

Fig 2.—Diastematomyelia.

Fig 3.—Dermal sinus.

Fig 4.—Occult dysraphic state presenting as hemangioma.

(*a*) Tethering of the spinal cord may take place in association with diastematomyelia (Fig 2), spinal dermal sinus (Fig 3), and cutaneous hemangioma with an underlying lesion of the spinal cord (Fig 4). Progressive neurologic deficits of the lower limbs and severe bladder dysfunction leading to hydronephrosis may occur.

(*b*) The most common solid tumor in neonates is a sacrococcygeal teratoma (Fig 1) presenting as a caudal mass within or below the intergluteal crease. This is in contrast to a lipomatous mass that lies above the intergluteal crease. Because it usually arises from the coccyx, the tumor spares the spinal column and canal. The incidence and severity of malignancy is related to the time of diagnosis, and, therefore, early recognition and total surgical excision of the mass is important.

(*c*) An increased incidence of meningitis occurs in patients with a dermal sinus tract that connects the external surface of the lumbosacral region with the vertebral canal (Fig 3). Early surgical removal of the sinus tract and its intraspinal extensions helps to prevent the occurrence of meningitis.

(*d*) Tumors or congenital cutaneous lesions, such as hemangiomas, located in the midline of the back increase the risk of the presence of associated spina bifida or extension of the lesion up or down the spinal column. Patients with such lesions should routinely undergo ultrasonography or other studies to determine if there is an extension of the tumor or the presence of spina bifida.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

CARNATION® INTRODUCES

NEW!

GOOD NATURE™

Iron Fortified Follow-Up Formula

For babies over six months of age
eating solid foods

NEW!

GOOD NATURE

Nutritionally completes baby's solid food diet

When baby reaches the solid food stage, approximately 6 months of age, formula is no longer his sole source of nutrition. Yet, the high-carbohydrate cereals, fruits, and vegetables he eats are low in certain nutrients. And, older babies require less energy from fat[1] and more from protein[2] So, Carnation developed GOOD NATURE Follow-Up Formula, specifically designed to complement the diet of babies who are routinely eating solid food.

GOOD NATURE makes good sense

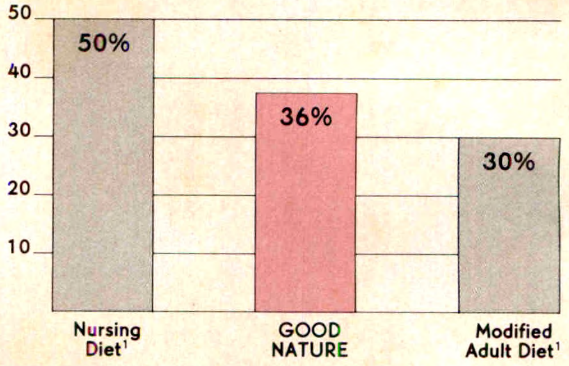
Unlike starter formula, GOOD NATURE is a follow-up formula that provides added nutrients for the older baby's optimal growth and development. GOOD NATURE contains more protein and calcium than starter formula to support the increased metabolic demands of bone mineralization and muscle mass growth.

The ratio of unsaturated to saturated fatty acids in GOOD NATURE is 2:1. GOOD NATURE is higher in monounsaturated fatty acids yet contains 28% less fat than starter formula to satisfy the changing needs of the older baby.

STAGES OF BABY FEEDING

Birth up to 6 months	6 months up to 12 months
NURSING DIET Mother's milk and/or starter formula	**TRANSITIONAL DIET** Mother's milk and/or GOOD NATURE* with cereals, fruits, vegetables *Not to replace breast milk. Use only when breast-feeding is not an option. Intended only for babies over 6 months of age eating solid foods.

Recommended Fat Intake†



†Percentage of total caloric intake. GOOD NATURE has an optimal fat blend that is high in monounsaturated fatty acids.

Protein Requirements During the First Year of Life[2]

Age	Average Weight, kg	Protein g/kg	Requirements per day, g
0-6 months	6.0	2.2	13.2
6-12 months	9.0	2.0	18.0

REFERENCES:

1. Kwiterovich PO Jr, Salz KM: Pediatric aspects of the diet-heart hypothesis, in Bond JT, Filer LJ, Leveille GA, et al (eds): *Infant and Child Feeding*. Academic Press, 1981, pp 283-315.

2. Food and Nutrition Board, NAS/MRC. *Recommended Dietary Allowances*, ed 9, 1980.

Follow Up Formula

Over 12 months
MODIFIED ADULT DIET Cow's milk and table food

Comparative Nutritional Analysis of GOOD NATURE Follow-Up Formula and Starter Formula

NUTRITION INFORMATION PER 100 CALORIES (5 FL OZ PREPARED AS DIRECTED)

	GOOD NATURE‡ Follow-Up Formula	Caloric Distribution (%)	Milk-Based Starter Formula§	Caloric Distribution (%)
NUTRIENTS:				
Protein	3.0 g	12.0	2.22 g	8.9
Fat	3.9 g	35.1	5.37 g	48.8
Carbohydrate	13.2 g	52.8	10.7 g	42.8
Water	134 g		133 g	
Linoleic Acid	700 mg		1,300 mg	
VITAMINS:				
Vitamin A	250 IU		300 IU	
Vitamin D	65 IU		60 IU	
Vitamin E	0.8 IU		3.0 IU	
Vitamin K	8.1 mcg		8 mcg	
Thiamine	80 mcg		100 mcg	
Riboflavin	96 mcg		150 mcg	
Vitamin B_6	66 mcg		60 mcg	
Vitamin B_{12}	0.32 mcg		0.25 mcg	
Niacin	1,280 mcg		1,050 mcg	
Folic Acid	16 mcg		15 mcg	
Pantothenic Acid	480 mcg		450 mcg	
Biotin	1.5 mcg		4.4 mcg	
Vitamin C	8 mg		9 mg	
MINERALS:				
Calcium	135 mg		75 mg	
Phosphorus	90 mg		58 mg	
Magnesium	8.4 mg		6 mg	
Iron	1.9 mg▼		1.8 mg▼	
Zinc	0.63 mg		0.75 mg	
Manganese	7 mcg		5 mcg	
Copper	76 mcg		90 mcg	
Iodine	5.7 mcg		15 mcg	
Sodium	39 mg		32 mg	
Potassium	135 mg		120 mg	
Chloride	90 mg		75 mg	

INGREDIENTS: ¶Ⓤ NONFAT DRY MILK, CORN SYRUP SOLIDS, PALM OIL, CORN OIL, HIGH-OLEIC SAFFLOWER OIL, CALCIUM PHOSPHATE, CALCIUM CITRATE, SOY LECITHIN, POTASSIUM CITRATE, SODIUM CITRATE, SODIUM ASCORBATE, FERROUS SULFATE, MAGNESIUM CHLORIDE, ZINC SULFATE, NIACINAMIDE, ALPHA TOCOPHERYL ACETATE, CALCIUM PANTOTHENATE, COPPER SULFATE, VITAMIN A ACETATE, THIAMINE MONONITRATE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE (VITAMIN K), POTASSIUM IODIDE, VITAMIN D_3, BIOTIN, VITAMIN B_{12}.

‡All nutrients, plus the renal solute load for GOOD NATURE, are within the range recommended by AAP/CON for older babies.

§Based on Similac® product labeling, Ross Laboratories, 1986.

▼The addition of iron to this formula conforms to the recommendation of AAP/CON.

¶Easy-to-mix powder. Ready-to-feed also contains water.

GOOD NATURE is good nutrition

GOOD NATURE also has a carbohydrate blend of 63% corn syrup solids and 37% lactose to help assure tolerance. It contains 12 mg iron per quart to help ensure a sufficient supply at an age when inborn stores are depleted. GOOD NATURE costs less than starter formula and also tastes, smells, and looks like the real food baby is learning to enjoy.

When baby is ready for solid food, Mom may ask you about GOOD NATURE Follow-Up Formula. You can reassure her that GOOD NATURE is nutritionally sound and makes good sense for her baby.

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GOOD NATURE Follow-Up Formula… now available to consumers in 32-fl-oz ready-to-feed fresh packs and 12-oz easy-to-mix powder canisters.

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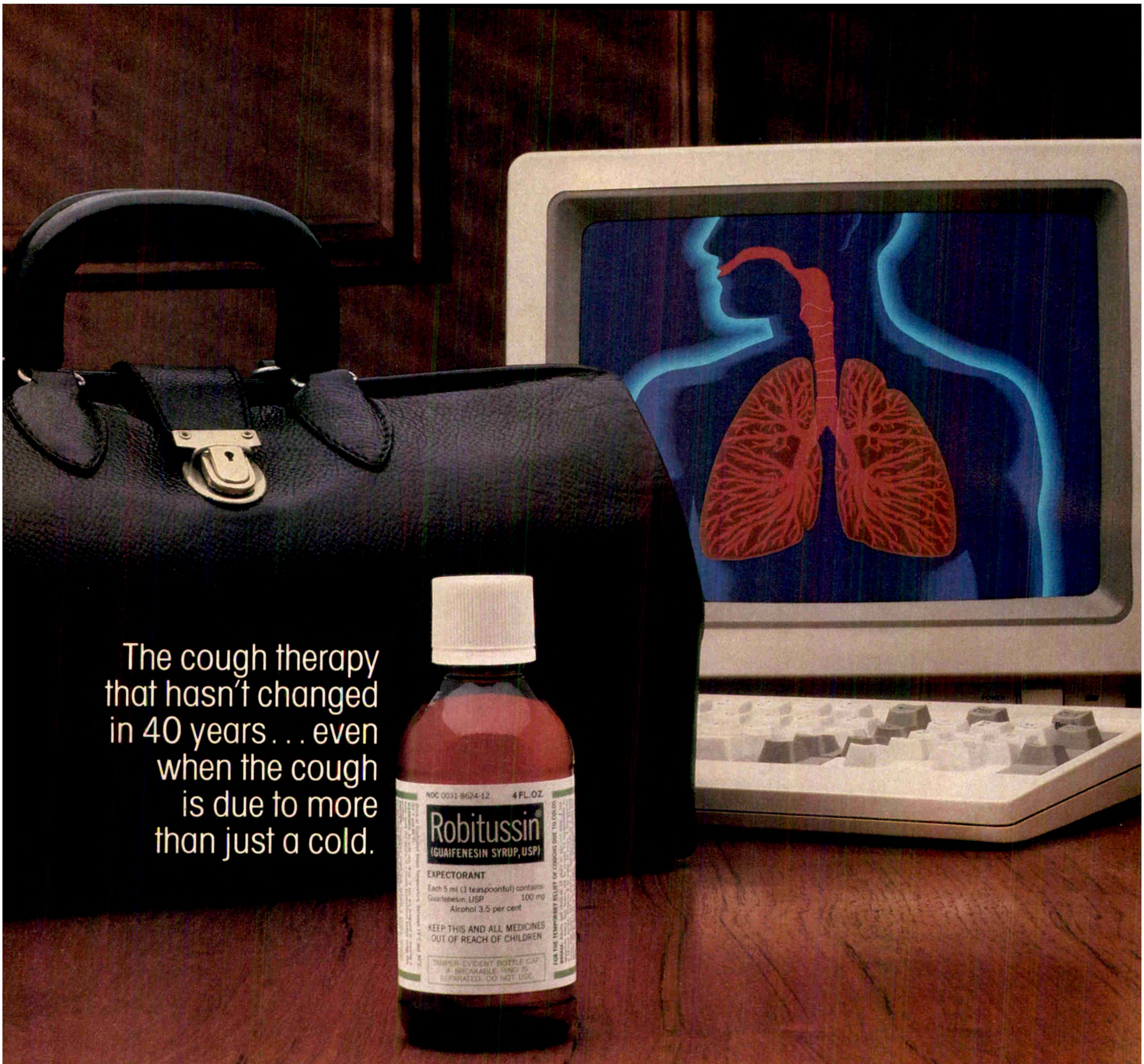

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AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOLUME 142

JANUARY THROUGH DECEMBER 1988

American Medical Association Publication

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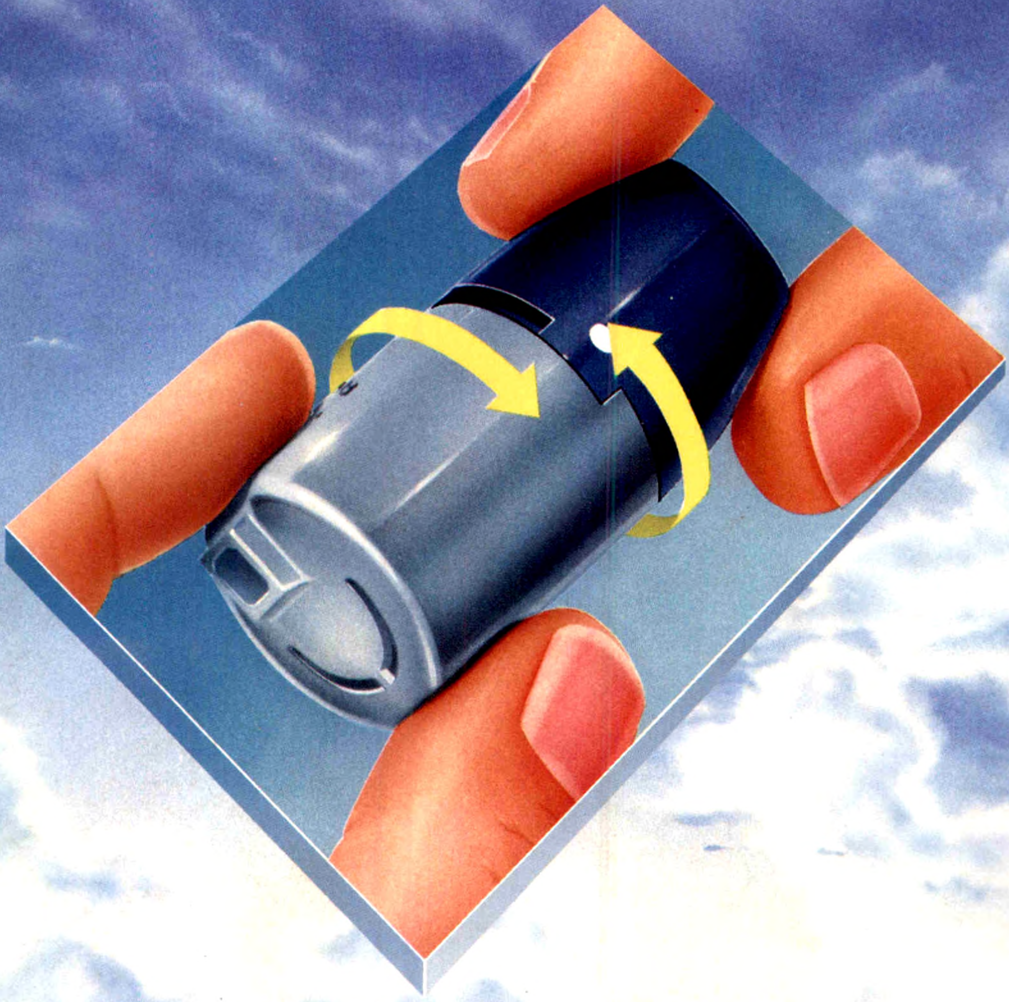

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